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L2 46456 L1 AND ANTIGEN PRESENTING CELL OR "APC"

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L3 27 L2 AND RETINOIDS

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L4 7 L3 AND CYTOKINE

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L5 ANSWER 1 OF 5 MEDLINE on STN DUPLICATE 1
2002687739 Document Number: 22335814. PubMed ID: 12444955. Protection against UV-induced suppression of contact hypersensitivity responses by sunscreens in humans. Cooper K D; Baron E D; LeVee G; Stevens S R. (Department of Dermatology and Skin Study Center, University Hospitals of Cleveland/Case Western Reserve University, Cleveland, OH, USA.) EXPERIMENTAL DERMATOLOGY, (2002) 11 Suppl 1 20-7. Ref: 42. Journal code: 9301549. ISSN: 0906-6705. Pub. country: Denmark. Language: English.

AB Both in vivo skin immune responses and the skin's reaction to sun exposure integrate a complex interplay of biologic responses. The complexity and multiplicity of events that occur in the skin during an immune response make it a sensitive indication of both UVB and UVA-induced changes in the skin by sun damage, as well as those changes that are prevented by various sunscreens. Sunscreens are the most effective and widely available intervention for sun damage, other than sun avoidance or clothing. However, sunscreens vary widely in their relative ability to screen various UV waveband components, and their testing has been variably applied to outcomes other than for erythema to determine the sunburn protection factor (SPF), a measure primarily of UVB filtration only. Determination of an immune protection factor (IPF) has been proposed as an alternative or adjunctive measure to SPF, and recent studies show IPF can indeed detect added in vivo functionality of sunscreens, such as high levels of UVA protection, that SPF cannot. Clarification of the definition of IPF, however, is required. Excellent data are available on quantification of the IPF for restoring the afferent or induction arm of contact sensitivity, but other immune parameters have also been measured. Proposed here is nomenclature for whether the IPF is measured using contact sensitivity induction (IPF-CS-I), contact sensitivity elicitation (IPF-CS-E), delayed-type hypersensitivity elicitation (IPF-DTH-E), antigen-presenting cell function (IPF-**APC**-FXN) or numbers (IPF-**APC**-#), and **cytokine** modification such as IL-10 (i.e. IPF-cyto-IL-10). Similar nomenclatures could be used for other measures of skin function protection (i.e. DNA damage, p53 induction, oxidation

products, etc.). A review of in vivo human studies, in which sunscreens are used to intervene in a UV-induced modulation of immune response, cells or **cytokines**, highlights the technical variables and statistical approaches which must also be standardized in the context of an IPF for regulatory or product claim purposes. Development of such IPF standards would allow the integration of both UVB and nonUVB (UVA, blue and possible IR) solar waveband effect-reversals, could be applied to integrate effects of other ingredients with protective function (i.e. antioxidants, **r tinoids**, or other novel products), and would spur development of more advanced and complete protection products.

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN

2001:545502 Document No. 135:117219 Hapten-coagulation agent-antineoplastic agent combinations for treating neoplasms. Yu, Baofa (USA). PCT Int. Appl. WO 2001052868 A1 20010726, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1737 20010118. PRIORITY: US 2000-PV177024 20000119.

AB Methods are provided for treating neoplasms, tumors and cancers, using one or more haptens and coagulation agents or treatments, alone or in combination with other anti-neoplastic agents or treatments. Also provided are combinations, and kits contg. the combinations for effecting the therapy.

L5 ANSWER 3 OF 5 MEDLINE on STN

2001683974 Document Number: 21587153. PubMed ID: 11729749. Cooperation of liver cells in health and disease. Kmiec Z. (Medical University of Gdansk, Department of Histology and Immunology, 80211 Gdansk, Poland.. zkmiec@amg.gda.pl) . ADVANCES IN ANATOMY, EMBRYOLOGY AND CELL BIOLOGY, (2001) 161 III-XIII, 1-151. Ref: 724. Journal code: 0407712. ISSN: 0301-5556. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB The liver lobule is formed by parenchymal cells, i.e., hepatocytes and nonparenchymal cells. In contrast to hepatocytes that occupy almost 80% of the total liver volume and perform the majority of numerous liver functions, nonparenchymal liver cells, which contribute only 6.5% to the liver volume, but 40% to the total number of liver cells, are localized in the sinusoidal compartment of the tissue. The walls of hepatic sinusoid are lined by three different cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells (HSC, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells). Additionally, intrahepatic lymphocytes (IHL), including pit cells, i.e., liver-specific natural killer cells, are often present in the sinusoidal lumen. It has been increasingly recognized that both under normal and pathological conditions, many hepatocyte functions are regulated by substances released from neighboring nonparenchymal cells. Liver sinusoidal endothelial cells constitute the lining or wall of the hepatic sinusoid. They perform important filtration function due to the presence of small fenestrations that allow free diffusion of many substances, but not of particles of the size of chylomicrons, between the blood and the hepatocyte surface. SEC show huge endocytic capacity for many ligands including glycoproteins, components of the extracellular matrix (ECM; such as hyaluronate, collagen fragments, fibronectin, or chondroitin sulphate proteoglycan), immune complexes, transferrin and ceruloplasmin. SEC may function as antigen-presenting cells (**APC**) in the context of both MHC-I and MHC-II restriction with the resulting development of antigen-specific T-cell tolerance. They are also active in the secretion of **cytokines**, eicosanoids (i.e., prostanoids and leukotrienes), endothelin-1, nitric oxide, and some ECM components.

Kupffer cells are intrasinusoidally located tissue macrophages with a pronounced endocytic and phagocytic capacity. They are in constant contact with gut-derived particulate materials and soluble bacterial products so that a subthreshold level of their activation in the normal liver may be anticipated. Hepatic macrophages secrete potent mediators of the inflammatory response (reactive oxygen species, eicosanoids, nitric oxide, carbon monoxide, TNF-alpha, and other **cytokines**), and thus control the early phase of liver inflammation, playing an important part in innate immune defense. High exposure of Kupffer cells to bacterial products, especially endotoxin (lipopolysaccharide, LPS), can lead to the intensive production of inflammatory mediators, and ultimately to liver injury. Besides typical macrophage activities, Kupffer cells play an important role in the clearance of senescent and damaged erythrocytes. Liver macrophages modulate immune responses via antigen presentation, suppression of T-cell activation by antigen-presenting sinusoidal endothelial cells via paracrine actions of IL-10, prostanoids, and TNF-alpha, and participation in the development of oral tolerance to bacterial superantigens. Moreover, during liver injury and inflammation, Kupffer cells secrete enzymes and **cytokines** that may damage hepatocytes, and are active in the remodeling of extracellular matrix. Hepatic stellate cells are present in the perisinusoidal space. They are characterized by abundance of intracytoplasmic fat droplets and the presence of well-branched cytoplasmic processes, which embrace endothelial cells and provide focally a double lining for sinusoid. In the normal liver HSC store vitamin A, control turnover of extracellular matrix, and regulate the contractility of sinusoids. Acute damage to hepatocytes activates transformation of quiescent stellate cells into myofibroblast-like cells that play a key role in the development of inflammatory fibrotic response. Pit cells represent a liver-associated population of large granular lymphocytes, i.e., natural killer (NK) cells. They spontaneously kill a variety of tumor cells in an MHC-unrestricted way, and this antitumor activity may be enhanced by the secretion of interferon-gamma. Besides pit cells, the adult liver contains other subpopulations of lymphocytes such as gamma delta T cells, and both "conventional" and "unconventional" alpha beta T cells, the latter containing liver-specific NK T cells. The development of methods for the isolation and culture of main liver cell types allowed to demonstrate that both nonparenchymal and parenchymal cells secrete tens of mediators that exert multiple paracrine and autocrine actions. Co-culture experiments and analyses of the effects of conditioned media on cultures of another liver cell type have enabled the identification of many substances released from non-parenchymal liver cells that evidently regulate some important functions of neighboring hepatocytes and non-hepatocytes. To the key mediators involved in the intercellular communication in the liver belong prostanoids, nitric oxide, endothelin-1, TNF-alpha, interleukins, and chemokines, many growth factors (TGF-beta, PDGF, IGF-I, HGF), and reactive oxygen species (ROS). Paradoxically, the cooperation of liver cells is better understood under some pathological conditions (i.e., in experimental models of liver injury) than in normal liver due to the possibility of comparing cellular phenotype under in vivo and in vitro conditions with the functions of the injured organ. The regulation of vitamin A metabolism provides an example of the physiological role for cellular cross-talk in the normal liver. The majority (up to 80%) of the total body vitamin A is stored in the liver as long-chain fatty acid esters of retinal, serving as the main source of **retinoids** that are utilized by all tissues throughout the body. Hepatocytes are directly involved in the uptake from blood of chylomicron remnants, and the synthesis of retinol-binding protein that transfers retinol to other tissues. However, more than 80% of the liver **r tinoids** are stored in lipid droplets of hepatic stellate cells. HSC are capable of both uptake and release of retinol depending on the body's retinol status. The activity of some major enzymes of vitamin A metabolism have been found to be many times higher per protein basis in stellate cells than in hepatocytes. Despite progress in the understanding of the roles played by these two cell types in hepatic retinoid metabolism, the way in which

retinoids move between the parenchymal cells, stellate cells, and blood plasma has not been fully elucidated. Sinusoidal blood flow is, to a great extent, regulated by hepatic stellate cells that can contract due to the presence of smooth muscle alpha-actin. The main vasoactive substances that affect constriction or relaxation of HSC derive both from distant sources and from neighboring hepatocytes (carbon monoxide, leukotrienes), endothelial cells (endothelin, nitric oxide, prostaglandins), Kupffer cells (prostaglandins, NO), and stellate cells themselves (endothelin, NO). The cellular cross-talk reflected by the fine-tuned modulation of sinusoidal contraction becomes disturbed under pathological conditions, such as endotoxemia or liver fibrosis, through the excess synthesis of vasoregulatory compounds and the involvement of additional mediators acting in a paracrine way. The liver is an important source of some growth factors and growth factor-binding proteins. Although hepatocytes synthesize the bulk of insulin-like growth factor I (IGF-I), also other types of nonparenchymal liver cells may produce this peptide. Cell-specific expression of distinct IGF-binding proteins observed in the rat and human liver provides the potential for specific regulation of hepatic IGF-I synthesis not only by growth hormone, insulin, and IGF-I, but also by **cytokines** released from activated Kupffer (IL-1, TNF-alpha, TGF-beta) or stellate cells (TGF-alpha, TGF-beta). Hepatic stellate cells may affect turnover of hepatocytes through the synthesis of potent positive as well as negative signals such as, respectively, hepatocyte-growth-factor or TGF-beta. Although hepatocytes seem not to produce TGF-beta, a pleiotropic **cytokine** synthesized and secreted in the latent form by Kupffer and stellate cells, they may contribute to its actions in the liver by the intracellular activation of latent TGF-beta, and secretion of the biologically active isoform. Many mediators that reach the liver during inflammatory processes, such as endotoxins, immune-complexes, anaphylatoxins, and PAF, increase glucose output in the perfused liver, but fail to do so in isolated hepatocytes, acting indirectly via prostaglandins released from Kupffer cells. In the liver, prostaglandins synthesized from arachidonic acid mainly in Kupffer cells in a response to various inflammatory stimuli, modulate hepatic glucose metabolism by increasing glycogenolysis in adjacent hepatocytes. The release of glucose from glycogen supports the increased demand for energetic fuel by the inflammatory cells such as leukocytes, and additionally enables enhanced glucose turnover in sinusoidal endothelial cells and Kupffer cells which is necessary for effective defense of these cells against invading microorganisms and oxidative stress in the liver. Leukotrienes, another oxidation product of arachidonic acid, have vasoconstrictive, cholestatic, and metabolic effects in the liver. A transcellular synthesis of cysteinyl leukotrienes (LTC4, LTD4, and LTE4) functions in the liver: LTA4, an important intermediate, is synthesized in Kupffer cells, taken up by hepatocytes, converted into the potent LTC4, and then released into extracellular space, acting in a paracrine way on Kupffer and sinusoidal endothelial cells. Thus, hepatocytes are target cells for the action of eicosanoids and the site of their transformation and degradation, but can not directly oxidate arachidonic acid to eicosanoids. (ABSTRACT TRUNCATED)

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN

1996:223149 Document No. 124:286610 Vitamin A down-regulation of IFN-.gamma. synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. Cantorna, Margherita T.; Nashold, Faye E.; Chun, Tae Yon; Hayes, Colleen E. (Dep. Biochem., Univ. Wisconsin-Madison, Madison, WI, 53706, USA). Journal of Immunology, 156(8), 2674-9 (English) 1996. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB Some infections deplete serum retinol, low retinol reduces immunity, and reduced immunity establishes susceptibility to further infection in a cyclical relation that is poorly understood. When retinol was low, there was excessive Th1 cell IFN-.gamma. synthesis and inadequate Th2 cell IL-4 and IL-5 synthesis. The retinol metabolite retinoic acid inhibited the IFN-.gamma. stimulatory activity of **APCs**, enhanced Th2 cell

differentiation, and inhibited Th1 cell IFN-.gamma. synthesis. Here the authors focus on the mechanism for retinoic acid inhibition of IFN-.gamma. synthesis in myelin basic protein-specific MM4 Th1 cells. Physiol. amts. of all-trans-retinoic acid directly and specifically down-regulated the MM4 Th1 cell IFN-.gamma. secretion rate in vitro without affecting cell growth, viability, or overall protein synthesis. All-trans-, 9-cis-, and 13-cis-retinoic acid, and the synthetic retinoid Ch55, inhibited IFN-.gamma. synthesis effectively, whereas retinaldehyde, retinol, and retinyl acetate did not. This pattern suggests retinoic acid receptor involvement in the inhibition mechanism. Retinoic acid did not inhibit when Th1 cells were activated only through the TCR/CD3 complex, with or without IL-2 costimulation. Retinoic acid inhibited IFN-.gamma. synthesis when the CD28 costimulatory pathway was activated in addn. to the TCR/CD3 pathway, suggesting it blocks some step in the CD28 pathway. Retinoid probably acted to decrease IFN-.gamma. transcript accumulation by decreasing transcription because it did not decrease transcript stability. The authors suggest that unrestrained IFN-.gamma. transcript accumulation by decreasing transcription because it did not decrease transcript stability. The authors suggest that unrestrained IFN-.gamma. synthesis is one key immunobiol. mechanism that accounts for poor antibody-mediated immunity in hypovitaminosis A, since IFN-.gamma. in relatively small amts. can limit Th2 cell growth and interfere with the B cell stimulatory functions of Th2 cell **cytokines**.

L5 ANSWER 5 OF 5 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998192162 EMBASE Differential induction of IL-12 p40 and IL-10 mRNA in human Langerhans' cells and keratinocytes by in vivo occlusion, vehicle, and all-TRANS retinoic acid. Chen G.; Kang K.; Kang S.; Rook A.H.; Kubin M.; Voorhees J.J.; Cooper K.D.. Dr. K.D. Cooper, Department of Dermatology, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106-5028, United States. Journal of Cutaneous Medicine and Surgery 1/2 (74-80) 1996.
Refs: 35.
ISSN: 1203-4754. CODEN: JCMSFU. Pub. Country: Canada. Language: English. Summary Language: English; French.

AB Background: Hydration and pharmacologic manipulation of the skin may have immunomodulatory effects. For instance, retinoic acid (RA) in vivo upregulates antigen-presenting cell (**APC**) activity of Langerhans' cells (LC). Objective: Our study was to determine whether RA increases LC **APC** activity via alteration of the potent immunoregulatory and reciprocally acting **cytokines**, IL-12 and IL-10. Methods: 0.1% RA and vehicle solvent only (V) as a control were applied under occlusion on the skin of normal volunteers. Freshly selected CD1a+ LC and keratinocytes from keratome were subject to semiquantitative determination of IL-12 p40 and IL-10 mRNA levels. IL-12 p40 protein was measured by radioimmunoassay. Results: Occlusion alone and open vehicle alone did not induce LC immunoregulatory **cytokines**; LCs demonstrated significant induction of IL-12 p40 mRNA, when the vehicle was occluded for 48 hours and, to a lesser extent, IL-10 as well. IL-12 p40 mRNA could be further induced by RA-LC at the 20-hour time point; however, IL-10 mRNA was induced at the 48-hour time point. Neither occlusion nor RA significantly induced IL-12 p40 or IL-10 mRNA in CD1a keratinocytes at any time points. Conclusion: A tight reciprocal regulation of IL-10 and IL-12 is present in LCs and is consistent with the initial, but self-limited, inflammatory effect of occlusion and topical **retinoids**.

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L6 ANSWER 1 OF 15 MEDLINE on STN

2002353984 Document Number: 22091948. PubMed ID: 12097298. Cyclin B and E2F-1 expression in prostate carcinoma cells treated with the novel retinoid CD437 are regulated by the ubiquitin-mediated pathway. Farhana Lulu; Dawson Marcia; Rishi Arun K; Zhang Yuxiang; Van Buren Eric; Trivedi Charu; Reichert Uwe; Fang Guowei; Kirschner Marc W; Fontana Joseph A. (John D. Dingell VA Medical Center and Karmanos Cancer Institute, and Department Internal Medicine, Wayne State University, Detroit, Michigan 48201, USA.) CANCER RESEARCH, (2002 Jul 1) 62 (13) 3842-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB E2F-1 and cyclin B are important regulators of the cell cycle, and their expressionand degradation are tightly regulated. Proteolysis of both molecules is mediated by the ubiquitin degradation pathway involving the activation of specific E3 ubiquitin ligases. Treatment of prostate carcinoma cells with the novel retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437/AHPN) results in the enhanced expression of E2F-1 and rapid degradation of cyclin B in the absence of the modulation of mRNA levels; this is accompanied by the S phase arrest of the cells and subsequent apoptosis. The elevated level of E2F-1 is because of the enhanced stability of the molecule, as indicated by pulse-labeling studies, demonstrating a prolonged half-life. The enhanced E2F-1 stability is associated with the concomitant acetylation of E2F-1, the disassociation of E2F-1 from the E2F-1 E3 ligase p45(SKP2), and decreased E2F-1 ubiquitination, suggesting CD437 inhibition of E-3 E2F-1 ligase activity. Exposure of the cells to CD437 also results in the enhanced association of the cyclin B E3 ligase **APC** with cyclin B and the rapid proteolysis of cyclin B. The CD437-enhanced proteolysis of cyclin B is blocked in the presence of the ubiquitin proteolysis inhibitor N-acetyl-leu-leu-norleu-al. Thus, CD437 modulates the expression of E2F-1 and cyclin B through the simultaneous stimulation and inhibition of the cyclin B and E2F-1 E3 ligases, respectively.

L6 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1

2002687739 Document Number: 22335814. PubMed ID: 12444955. Protection against UV-induced suppression of contact hypersensitivity responses by sunscreens in humans. Cooper K D; Baron E D; LeVee G; Stevens S R. (Department of Dermatology and Skin Study Center, University Hospitals of Cleveland/Case Western Reserve University, Cleveland, OH, USA.) EXPERIMENTAL DERMATOLOGY, (2002) 11 Suppl 1 20-7. Ref: 42. Journal code: 9301549. ISSN: 0906-6705. Pub. country: Denmark. Language: English.

AB Both in vivo skin immune responses and the skin's reaction to sun exposure integrate a complex interplay of biologic responses. The complexity and multiplicity of events that occur in the skin during an immune response make it a sensitive indication of both UVB and UVA-induced changes in the skin by sun damage, as well as those changes that are prevented by various sunscreens. Sunscreens are the most effective and widely available intervention for sun damage, other than sun avoidance or clothing. However, sunscreens vary widely in their relative ability to screen various UV waveband components, and their testing has been variably applied to outcomes other than for erythema to determine the sunburn protection factor (SPF), a measure primarily of UVB filtration only. Determination of an immune protection factor (IPF) has been proposed as an alternative or adjunctive measure to SPF, and recent studies show IPF can indeed detect added in vivo functionality of sunscreens, such as high levels of UVA protection, that SPF cannot. Clarification of the definition of IPF, however, is required. Excellent data are available on quantification of the IPF for restoring the afferent or induction arm of contact sensitivity, but other immune parameters have also been measured. Proposed here is nomenclature for whether the IPF is measured using contact sensitivity induction (IPF-CS-I), contact sensitivity elicitation (IPF-CS-E), delayed-type hypersensitivity elicitation (IPF-DTH-E), antigen-presenting cell function (IPF-**APC**-FXN) or numbers (IPF-**APC**-#), and cytokine modification such as IL-10 (i.e. IPF-cyto-IL-10). Similar nomenclatures could be used for other measures

of skin function protection (i.e. DNA damage, p53 induction, oxidation products, etc.). A review of in vivo human studies, in which sunscreens are used to intervene in a UV-induced modulation of immune response, cells or cytokines, highlights the technical variables and statistical approaches which must also be standardized in the context of an IPF for regulatory or product claim purposes. Development of such IPF standards would allow the integration of both UVB and nonUVB (UVA, blue and possible IR) solar waveband effect-reversals, could be applied to integrate effects of other ingredients with protective function (i.e. antioxidants, **r tinoids**, or other novel products), and would spur development of more advanced and complete protection products.

L6 ANSWER 3 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:96671 Document No.: PREV200200096671. Expression of surface CD40 and immunocytochemical actin-bundling protein fascin in dendritic cells from multiple myeloma treated with **retinoids** during their differentiation in vitro. Chiriva-Internati, Maurizio [Reprint author]; Grizzi, Fabio [Reprint author]; Franceschini, Barbara; Hermonat, Paul L.; Lim, Seah; Dioguardi, Nicola. Scientific Direction, Istituto Clinico Humanitas, Via Manzoni 56, Rozzano, 20089, Milano, Italy. fabio.grizzi@humanitas.it. In Vitro Cellular and Developmental Biology Animal, (November-December, 2001) Vol. 37, No. 10, pp. 641-643. print. ISSN: 1071-2690. Language: English.

L6 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
2001:545502 Document No. 135:117219 Hapten-coagulation agent-antineoplastic agent combinations for treating neoplasms. Yu, Baofa (USA). PCT Int. Appl. WO 2001052868 A1 20010726, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1737 20010118. PRIORITY: US 2000-PV177024 20000119.

AB Methods are provided for treating neoplasms, tumors and cancers, using one or more haptens and coagulation agents or treatments, alone or in combination with other anti-neoplastic agents or treatments. Also provided are combinations, and kits contg. the combinations for effecting the therapy.

L6 ANSWER 5 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:209933 Document No.: PREV200200209933. Retinoic acid and CD40 ligand co-operate to promote induction of immune accessory molecules and immune responses to human myeloid leukemia cells. Kato, Kazunori [Reprint author]; Yoshida, Mitsuzi [Reprint author]; Takaue, Yoichi [Reprint author]; Kipps, Thomas J.; Wakasugi, Hiro [Reprint author]. Pharmacology Div., Natl. Cancer Ctr. Res. Inst., Chuoku, Tokyo, Japan. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 589a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB We and others have reported that agonistic anti-CD40 Ab or CD40-ligand (CD40L) transfected cells could induce neoplastic B cells, including chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), or acute lymphoblastic leukemia (ALL), to become effective antigen presenting cells (**APCs**) in vitro and in vivo. To extend these practical strategies into patients with other leukemia such as chronic myelogenous leukemia (CML) and acute myeloid leukemia (AML), we examined whether ligation of CD40 on myeloid leukemia could induce changes in the leukemia phenotype that could facilitate T cell immune recognition. Leukemic B cells treated with CD40L were induced to express higher levels of CD80,

CD83 and CD86 than untreated leukemia, while these phenotypic changes induced by CD40L are not found in human promyelocytic, myeloblastic and monocytic leukemia cells that are negative or moderate positive for CD40. To induce these myeloid leukemia cells to be susceptible to CD40 ligation, we treated these cells with differentiation-inducing reagents and tested for the expression of CD40. A treatment of CD40-negative as wells as CD40-positive myeloid leukemia with all-trans retinoic acid (ATRA) and 9-cis retinoic acid (9-cis RA), but not with vitamin D3, induces a significant increase in the expression of CD40 in time-dependent manner. In addition, the expression of other differentiation antigens (CD11b and CD11c) and immune accessory molecules (CD54 and CD86) are also augmented by ATRA. Importantly, engagement of CD40 on ATRA-treated myeloid leukemia by CD40L results in the leukemia cells expressing heretofore non-expressed costimulatory molecules, such as CD80 and CD83. Furthermore, these myeloid leukemia cells treated with ATRA plus CD40L are highly effective stimulators in mixed lymphocyte-leukemia responses and can induce production of IFN-gamma by T cells. Overall, these results reveal that stimulation with **retinoids** combined with CD40L is a novel approach for the induction of **APC** phenotype and function in human myeloid leukemia that should be useful in eliciting anti-leukemia immune responses.

L6 ANSWER 6 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

2001:886358 The Genuine Article (R) Number: 487XN. Leiden mutation (as genetic) and environmental (**retinoids**) sequences in the acute and chronic inflammatory and premalignant colon disease in human gastrointestinal tract. Mozsik G (Reprint); Nagy Z; Nagy A; Rumi G; Karadi O; Czimmer J; Matus Z; Toth G; Par A. Univ Pecs, Fac Med, Dept Med 1, H-7643 Pecs, Hungary (Reprint); Univ Pecs, Fac Med, Dept Med Chem, H-7643 Pecs, Hungary. JOURNAL OF PHYSIOLOGY-PARIS (JAN-DEC 2001) Vol. 95, No. 1-6, Sp. iss. SI, pp. 489-494. Publisher: EDITIONS SCIENTIFIQUES MEDICALES ELSEVIER. 23 RUE LINOIS, 75724 PARIS CEDEX 15, FRANCE. ISSN: 0928-4257. Pub. country: Hungary. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Tumor, calor, dolor, pallor and functio laesa are together involved in the different acute and chronic inflammatory processes. The processes involved in the inflammation are determined by differently acquired and hereditary factors. Recently the presence of a new genetic marker (Leiden point mutation) was found in Crohn's disease and ulcerative colitis. On the other hand, the GI mucosal integrity was proven on gastrointestinal mucosal damage to be produced by different chemicals, xenobiotics, drugs. In human observations, the serum level of **r tinoids** (vitamin A, lutein, zeaxanthin, alpha-, beta -carotene) was proven in patients with chronic gastrointestinal inflammatory bowel disease. The aims of this study were (1) to measure the prevalence of Leiden mutation; (2) to identify the changes in the serum retinoid level in patients with Helicobacter pylori infection of the stomach (n = 24), hepatitis C infection (n = 75), ileitis terminalis (Crohn's disease, n = 49), ulcerative colitis (n = 35), colon polyposis (n = 59) and adenocarcinoma in colon polyps (n = 9), and 57 healthy persons were used in the control group, (3) to compare the directions of the changes in the measured parameters in the acute (H. pylori and hepatitis C infections), chronic (ileitis terminalis, ulcerative colitis) GI inflammatory diseases and in colon polyposis without and with malignisation. Methods: The Leiden mutation was measured by the method of polimerase chain reaction, the retinoid level in the patient's serum was measured by high liquid cromathografic method (HPCL). Results: (1) It has been found that the prevalence of Leiden mutation increased significantly in patients with ileitis terminalis ($P < 0.001$), ulcerative colitis ($P < 0.001$), colon polyposis ($P < 0.001$) and with colon polyps with malignisation ($P < 0.01$). (2) Serum level of vitamin A and zeaxantin were decreased significantly in all group of patients except for the group with H. pylori infections. (3) alpha- and beta -carotenes were found to be practically at the same level as those in the control groups, except in patients of colon polyps with malignisation. (4) The vitamin A, lutein, zeaxantin, alpha- and beta

-carotenes were decreased in patients with ileitis terminalis. Conclusions: (1) The essential role of **retinoids** (carotenoids) as environmental factors are suggested for keeping GI mucosal integrity in human healthy subjects and patients. (2) Leiden mutation, as a genetic marker, can be used in the screening of patients with ileitis terminalis, ulcerative colitis and colon polyposis (without and with malignisation). (3) An opposite direction can be found between the increased prevalence of Leiden mutation and decrease of serum levels of **retinoids** in group of patients with ileitis terminalis, ulcerative colitis and colon polyposis (without and with malignisation).

L6 ANSWER 7 OF 15 MEDLINE on STN

2001683974 Document Number: 21587153. PubMed ID: 11729749. Cooperation of liver cells in health and disease. Kmiec Z. (Medical University of Gdansk, Department of Histology and Immunology, 80211 Gdansk, Poland.. zkmiec@amg.gda.pl) . ADVANCES IN ANATOMY, EMBRYOLOGY AND CELL BIOLOGY, (2001) 161 III-XIII, 1-151. Ref: 724. Journal code: 0407712. ISSN: 0301-5556. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB The liver lobule is formed by parenchymal cells, i.e., hepatocytes and nonparenchymal cells. In contrast to hepatocytes that occupy almost 80% of the total liver volume and perform the majority of numerous liver functions, nonparenchymal liver cells, which contribute only 6.5% to the liver volume, but 40% to the total number of liver cells, are localized in the sinusoidal compartment of the tissue. The walls of hepatic sinusoid are lined by three different cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells (HSC, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells). Additionally, intrahepatic lymphocytes (IHL), including pit cells, i.e., liver-specific natural killer cells, are often present in the sinusoidal lumen. It has been increasingly recognized that both under normal and pathological conditions, many hepatocyte functions are regulated by substances released from neighboring nonparenchymal cells. Liver sinusoidal endothelial cells constitute the lining or wall of the hepatic sinusoid. They perform important filtration function due to the presence of small fenestrations that allow free diffusion of many substances, but not of particles of the size of chylomicrons, between the blood and the hepatocyte surface. SEC show huge endocytic capacity for many ligands including glycoproteins, components of the extracellular matrix (ECM; such as hyaluronate, collagen fragments, fibronectin, or chondroitin sulphate proteoglycan), immune complexes, transferrin and ceruloplasmin. SEC may function as antigen-presenting cells (**APC**) in the context of both MHC-I and MHC-II restriction with the resulting development of antigen-specific T-cell tolerance. They are also active in the secretion of cytokines, eicosanoids (i.e., prostanoids and leukotrienes), endothelin-1, nitric oxide, and some ECM components. Kupffer cells are intrasinusoidally located tissue macrophages with a pronounced endocytic and phagocytic capacity. They are in constant contact with gut-derived particulate materials and soluble bacterial products so that a subthreshold level of their activation in the normal liver may be anticipated. Hepatic macrophages secrete potent mediators of the inflammatory response (reactive oxygen species, eicosanoids, nitric oxide, carbon monoxide, TNF-alpha, and other cytokines), and thus control the early phase of liver inflammation, playing an important part in innate immune defense. High exposure of Kupffer cells to bacterial products, especially endotoxin (lipopolysaccharide, LPS), can lead to the intensive production of inflammatory mediators, and ultimately to liver injury. Besides typical macrophage activities, Kupffer cells play an important role in the clearance of senescent and damaged erythrocytes. Liver macrophages modulate immune responses via antigen presentation, suppression of T-cell activation by antigen-presenting sinusoidal endothelial cells via paracrine actions of IL-10, prostanoids, and TNF-alpha, and participation in the development of oral tolerance to bacterial superantigens. Moreover, during liver injury and inflammation,

Kupffer cells secrete enzymes and cytokines that may damage hepatocytes, and are active in the remodeling of extracellular matrix. Hepatic stellate cells are present in the perisinusoidal space. They are characterized by abundance of intracytoplasmic fat droplets and the presence of well-branched cytoplasmic processes, which embrace endothelial cells and provide focally a double lining for sinusoid. In the normal liver HSC store vitamin A, control turnover of extracellular matrix, and regulate the contractility of sinusoids. Acute damage to hepatocytes activates transformation of quiescent stellate cells into myofibroblast-like cells that play a key role in the development of inflammatory fibrotic response. Pit cells represent a liver-associated population of large granular lymphocytes, i.e., natural killer (NK) cells. They spontaneously kill a variety of tumor cells in an MHC-unrestricted way, and this antitumor activity may be enhanced by the secretion of interferon-gamma. Besides pit cells, the adult liver contains other subpopulations of lymphocytes such as gamma delta T cells, and both "conventional" and "unconventional" alpha beta T cells, the latter containing liver-specific NK T cells. The development of methods for the isolation and culture of main liver cell types allowed to demonstrate that both nonparenchymal and parenchymal cells secrete tens of mediators that exert multiple paracrine and autocrine actions. Co-culture experiments and analyses of the effects of conditioned media on cultures of another liver cell type have enabled the identification of many substances released from non-parenchymal liver cells that evidently regulate some important functions of neighboring hepatocytes and non-hepatocytes. To the key mediators involved in the intercellular communication in the liver belong prostanoids, nitric oxide, endothelin-1, TNF-alpha, interleukins, and chemokines, many growth factors (TGF-beta, PDGF, IGF-I, HGF), and reactive oxygen species (ROS). Paradoxically, the cooperation of liver cells is better understood under some pathological conditions (i.e., in experimental models of liver injury) than in normal liver due to the possibility of comparing cellular phenotype under in vivo and in vitro conditions with the functions of the injured organ. The regulation of vitamin A metabolism provides an example of the physiological role for cellular cross-talk in the normal liver. The majority (up to 80%) of the total body vitamin A is stored in the liver as long-chain fatty acid esters of retinal, serving as the main source of **retinoids** that are utilized by all tissues throughout the body. Hepatocytes are directly involved in the uptake from blood of chylomicron remnants, and the synthesis of retinol-binding protein that transfers retinol to other tissues. However, more than 80% of the liver **retinoids** are stored in lipid droplets of hepatic stellate cells. HSC are capable of both uptake and release of retinol depending on the body's retinol status. The activity of some major enzymes of vitamin A metabolism have been found to be many times higher per protein basis in stellate cells than in hepatocytes. Despite progress in the understanding of the roles played by these two cell types in hepatic retinoid metabolism, the way in which **retinoids** move between the parenchymal cells, stellate cells, and blood plasma has not been fully elucidated. Sinusoidal blood flow is, to a great extent, regulated by hepatic stellate cells that can contract due to the presence of smooth muscle alpha-actin. The main vasoactive substances that affect constriction or relaxation of HSC derive both from distant sources and from neighboring hepatocytes (carbon monoxide, leukotrienes), endothelial cells (endothelin, nitric oxide, prostaglandins), Kupffer cells (prostaglandins, NO), and stellate cells themselves (endothelin, NO). The cellular cross-talk reflected by the fine-tuned modulation of sinusoidal contraction becomes disturbed under pathological conditions, such as endotoxemia or liver fibrosis, through the excess synthesis of vasoregulatory compounds and the involvement of additional mediators acting in a paracrine way. The liver is an important source of some growth factors and growth factor-binding proteins. Although hepatocytes synthesize the bulk of insulin-like growth factor I (IGF-I), also other types of nonparenchymal liver cells may produce this peptide. Cell-specific expression of distinct IGF-binding proteins observed in the rat and human liver provides the potential for specific

regulation of hepatic IGF-I synthesis not only by growth hormone, insulin, and IGF-I, but also by cytokines released from activated Kupffer (IL-1, TNF-alpha, TGF-beta) or stellate cells (TGF-alpha, TGF-beta). Hepatic stellate cells may affect turnover of hepatocytes through the synthesis of potent positive as well as negative signals such as, respectively, hepatocyte-growth-factor or TGF-beta. Although hepatocytes seem not to produce TGF-beta, a pleiotropic cytokine synthesized and secreted in the latent form by Kupffer and stellate cells, they may contribute to its actions in the liver by the intracellular activation of latent TGF-beta, and secretion of the biologically active isoform. Many mediators that reach the liver during inflammatory processes, such as endotoxins, immune-complexes, anaphylatoxins, and PAF, increase glucose output in the perfused liver, but fail to do so in isolated hepatocytes, acting indirectly via prostaglandins released from Kupffer cells. In the liver, prostaglandins synthesized from arachidonic acid mainly in Kupffer cells in a response to various inflammatory stimuli, modulate hepatic glucose metabolism by increasing glycogenolysis in adjacent hepatocytes. The release of glucose from glycogen supports the increased demand for energetic fuel by the inflammatory cells such as leukocytes, and additionally enables enhanced glucose turnover in sinusoidal endothelial cells and Kupffer cells which is necessary for effective defense of these cells against invading microorganisms and oxidative stress in the liver. Leukotrienes, another oxidation product of arachidonic acid, have vasoconstrictive, cholestatic, and metabolic effects in the liver. A transcellular synthesis of cysteinyl leukotrienes (LTC4, LTD4, and LTE4) functions in the liver: LTA4, an important intermediate, is synthesized in Kupffer cells, taken up by hepatocytes, converted into the potent LTC4, and then released into extracellular space, acting in a paracrine way on Kupffer and sinusoidal endothelial cells. Thus, hepatocytes are target cells for the action of eicosanoids and the site of their transformation and degradation, but can not directly oxidate arachidonic acid to eicosanoids. (ABSTRACT TRUNCATED)

L6 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

2000:98244 Document No. 132:141708 Novel uses of ascorbyl-phosphoryl-cholesterol and compositions for practicing same. Ptchelintsev, Dmitri; Duffy, John A.; Kalafsky, Robert; Pahlck, Harold E. (Avon Products, Inc., USA). PCT Int. Appl. WO 2000006091 A1 20000210, 36 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US17420 19990730. PRIORITY: US 1998-126191 19980730; US 1998-189368 19981109.

AB The present invention relates to the use of 3'-(L-ascorbyl-2-O-phosphoryl)-cholesterol, 3'-(L-ascorbyl-3-O-phosphoryl)-cholesterol, and their derivs. ("**APC** compds."). More specifically, the present invention relates to use of **APC** compds. to improve the appearance and health of skin, hair, lips and nails. The present invention also relates to methods of topically administering **APC** compds. to cleanse skin and remove make-up, moisturize skin, enhance the shine and wear of nail coating compns., and to improve compns. having pigments and/or iron oxides. Addnl. novel uses of **APC** compds. provided by the present invention include a method of reducing epidermal synthesis of abnormal elastin, esp. epidermal synthesis of abnormal elastin that results from exposure to UV radiation. Also disclosed are novel methods of stimulating keratinocyte formation of triglycerides and achieving antioxidant activity in the skin by topically applying **APC** compds.

L6 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

2000:891464 Document No. 134:46650 Uses of ascorbyl-phosphoryl-cholesterol

for topical compositions. Ptchelintsev, Dmitri; Duffy, John A.; Kalafsky, Robert; Pahlck, Harold E. (Avon Products, Inc., USA). U.S. US 6162450 A 20001219, 6 pp., Cont.-in-part of U.S. 5,922,335. (English). CODEN: USXXAM. APPLICATION: US 1998-189368 19981109. PRIORITY: US 1995-440765 19950515; US 1997-837282 19970411; US 1997-853271 19970509; US 1998-126191 19980730.

AB The present invention relates to the use of 3'-(L-ascorbyl-2-o-phosphoryl)-cholesterol, 3'-(L-ascorbyl-3-o-phosphoryl)-cholesterol, and their derivs. (**APC** *compds.*). More specifically, the present invention relates to use of **APC** compds. to improve the appearance and health of skin, hair, lips and nails. The present invention also relates to methods of topically administering **APC** compds. to cleanse skin and remove make-up, moisturize skin, enhance the shine and wear of nail coating compns., and to improve compns. having pigments and/or iron oxides.

L6 ANSWER 10 OF 15 MEDLINE on STN DUPLICATE 2

2000187948 Document Number: 20187948. PubMed ID: 10720773. Use of transgenic mice in identifying chemopreventive agents. Alexander J. (Department of Environmental Medicine, National Institute of Public Health, 0403, Oslo, Norway.. jan.alexander@folkehelsa.no) . TOXICOLOGY LETTERS, (2000 Mar 15) 112-113 507-12. Ref: 49. Journal code: 7709027. ISSN: 0378-4274. Pub. country: Netherlands. Language: English.

AB Cancer chemoprevention uses natural- or synthetic chemical compounds to reverse, suppress or to prevent one or more of the biological events leading to the development of cancer. Chemopreventive agents are classified as blocking or suppressing according to their action on either the initiation or promotion-progression phases in experimental models using carcinogen treated animals. Transgenic animal technology has resulted in a plethora of murine models for cancer research providing insight into the complex oncogenic events contributing to the loss of cell cycle control and tumourigenesis. Transgenic models also offer an important opportunity to identify and study both tumourigens and chemopreventive agents. However, so far chemoprevention has in such models only been investigated to a limited degree and primarily in models with inactivated tumour suppressor genes. Studies show that spontaneous tumour developing due to loss of p53 function may be offset by preventive measures. The preventive actions of **retinoids** and polyamine synthesis inhibitors have been studied in the PIM mouse susceptible to lymphoma development. Most chemopreventive studies have been performed on murine familial adenomatous polyposis (FAP) models, which carry one non-functional **apc** gene and develop multiple intestinal adenomas upon inactivation of the wild type allele. Particularly non-steroidal anti-inflammatory drugs NSAIDs, which block COX-2, but also food components such as n-3 fatty acids show promising chemopreventive effects in these models. Transgenic cancer models demonstrate a strong gene-environment interaction, which is promising for the development of chemopreventive strategies.

L6 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 3

2000076866 Document Number: 20076866. PubMed ID: 10607566. Cross-regulation of beta-catenin-LEF/TCF and retinoid signaling pathways. Easwaran V; Pishvaian M; Salimuddin; Byers S. (Departments of Oncology and Cell Biology, The Lombardi Cancer Center, Georgetown University, Washington D.C., 20007, USA.) CURRENT BIOLOGY, (1999 Dec 2) 9 (23) 1415-8. Journal code: 9107782. ISSN: 0960-9822. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vitamin A derivatives (**retinoids**) are potent regulators of embryogenesis, cell proliferation, epithelial cell differentiation and carcinogenesis [1]. In breast cancer cells, the effects of **retinoids** are associated with changes in the cadherin-beta-catenin adhesion and signaling system [2] [3]. beta-catenin is a component of the Wnt signaling pathway, which regulates several developmental pathways [4]. Increases in cytoplasmic beta-catenin and beta-catenin signaling are also associated with numerous cancers, and are particularly important in colon

cancer [5]. The oncogenic and developmental effects of beta-catenin are mediated by its interaction with and activation of members of the LEF/TCF family of transcription factors [6] [7] [8]. Here, we shown that retinoic acid (RA) decreases the activity of the beta-catenin-LEF/TCF signaling pathway. This activity of RA was independent of the adenomatous polyposis coli (**APC**) tumor suppressor and ubiquitination-dependent degradation of cytoplasmic beta-catenin. Consistent with this finding, beta-catenin interacted directly with the RA receptor (RAR) in a retinoid-dependent manner, but not with the retinoid X receptor (RXR), and RAR competed with TCF for beta-catenin binding. The activity of RA on RAR-responsive promoters was also potentiated by beta-catenin. The data suggest that direct regulation of beta-catenin-LEF/TCF signaling is one mechanism whereby RA influences development, cell differentiation and cancer.

L6 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

1996:223149 Document No. 124:286610 Vitamin A down-regulation of IFN-.gamma. synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. Cantorna, Margherita T.; Nashold, Faye E.; Chun, Tae Yon; Hayes, Colleen E. (Dep. Biochem., Univ. Wisconsin-Madison, Madison, WI, 53706, USA). Journal of Immunology, 156(8), 2674-9 (English) 1996. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB Some infections deplete serum retinol, low retinol reduces immunity, and reduced immunity establishes susceptibility to further infection in a cyclical relation that is poorly understood. When retinol was low, there was excessive Th1 cell IFN-.gamma. synthesis and inadequate Th2 cell IL-4 and IL-5 synthesis. The retinol metabolite retinoic acid inhibited the IFN-.gamma. stimulatory activity of **APCs**, enhanced Th2 cell differentiation, and inhibited Th1 cell IFN-.gamma. synthesis. Here the authors focus on the mechanism for retinoic acid inhibition of IFN-.gamma. synthesis in myelin basic protein-specific MM4 Th1 cells. Physiol. amts. of all-trans-retinoic acid directly and specifically down-regulated the MM4 Th1 cell IFN-.gamma. secretion rate in vitro without affecting cell growth, viability, or overall protein synthesis. All-trans-, 9-cis-, and 13-cis-retinoic acid, and the synthetic retinoid Ch55, inhibited IFN-.gamma. synthesis effectively, whereas retinaldehyde, retinol, and retinyl acetate did not. This pattern suggests retinoic acid receptor involvement in the inhibition mechanism. Retinoic acid did not inhibit when Th1 cells were activated only through the TCR/CD3 complex, with or without IL-2 costimulation. Retinoic acid inhibited IFN-.gamma. synthesis when the CD28 costimulatory pathway was activated in addn. to the TCR/CD3 pathway, suggesting it blocks some step in the CD28 pathway. Retinoid probably acted to decrease IFN-.gamma. transcript accumulation by decreasing transcription because it did not decrease transcript stability. The authors suggest that unrestrained IFN-.gamma. transcript accumulation by decreasing transcription because it did not decrease transcript stability. The authors suggest that unrestrained IFN-.gamma. synthesis is one key immunobiol. mechanism that accounts for poor antibody-mediated immunity in hypovitaminosis A, since IFN-.gamma. in relatively small amts. can limit Th2 cell growth and interfere with the B cell stimulatory functions of Th2 cell cytokines.

L6 ANSWER 13 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998192162 EMBASE Differential induction of IL-12 p40 and IL-10 mRNA in human Langerhans' cells and keratinocytes by in vivo occlusion, vehicle, and all-TRANS retinoic acid. Chen G.; Kang K.; Kang S.; Rook A.H.; Kubin M.; Voorhees J.J.; Cooper K.D.. Dr. K.D. Cooper, Department of Dermatology, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106-5028, United States. Journal of Cutaneous Medicine and Surgery 1/2 (74-80) 1996.

Refs: 35.

ISSN: 1203-4754. CODEN: JCMSFU. Pub. Country: Canada. Language: English. Summary Language: English; French.

AB Background: Hydration and pharmacologic manipulation of the skin may have immunomodulatory effects. For instance, retinoic acid (RA) in vivo upregulates antigen-presenting cell (**APC**) activity of Langerhans' cells (LC). Objective: Our study was to determine whether RA increases LC **APC** activity via alteration of the potent immunoregulatory and reciprocally acting cytokines, IL-12 and IL-10. Methods: 0.1% RA and vehicle solvent only (V) as a control were applied under occlusion on the skin of normal volunteers. Freshly selected CD1a+ LC and keratinocytes from keratome were subject to semiquantitative determination of IL-12 p40 and IL-10 mRNA levels. IL-12 p40 protein was measured by radioimmunoassay. Results: Occlusion alone and open vehicle alone did not induce LC immunoregulatory cytokines; LCs demonstrated significant induction of IL-12 p40 mRNA, when the vehicle was occluded for 48 hours and, to a lesser extent, IL-10 as well. IL-12 p40 mRNA could be further induced by RA-LC at the 20-hour time point; however, IL-10 mRNA was induced at the 48-hour time point. Neither occlusion nor RA significantly induced IL-12 p40 or IL-10 mRNA in CD1a keratinocytes at any time points. Conclusion: A tight reciprocal regulation of IL-10 and IL-12 is present in LCs and is consistent with the initial, but self-limited, inflammatory effect of occlusion and topical **retinoids**.

L6 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 4
96114043 Document Number: 96114043. PubMed ID: 8672984. Genetic and cellular changes in colorectal cancer: proposed targets of chemopreventive agents. Greenwald P; Kelloff G J; Boone C W; McDonald S S. (Division of Cancer Prevention and Control, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.) CANCER EPIDEMIOLOGY, BIOMARKERS AND PREVENTION, (1995 Oct-Nov) 4 (7) 691-702. Ref: 175. Journal code: 9200608. ISSN: 1055-9965. Pub. country: United States. Language: English.

AB Progress in development of a genetic model for colorectal tumorigenesis and human chemoprevention research may allow the mechanism-based identification of targets and chemopreventive agents that will protect against colorectal cancer. For example, numerous mutagenic events can occur throughout colorectal carcinogenesis, including loss of heterozygosity in tumor suppressor genes such as **APC**, MCC, DCC, and p53, as well as in oncogenes such as K-ras. Chemopreventive agents that inhibit mutagenic activity such as N-acetyl-l-cysteine, oltipraz, and nonsteroidal anti-inflammatory drugs may protect against these mutations. Also, agents such as perillyl alcohol and lovastatin that interfere with protein isoprenylation and, hence, inhibit oncogene activation may protect against aberrant K-ras expression. Hyperproliferation in normal mucosa, leading to growth and progression of neoplasia, are also aspects of colorectal carcinogenesis that can be controlled by chemopreventive agents. Calcium is a chemopreventive agent for which there is both clinical and experimental evidence of inhibition of cell proliferation in colon mucosa. Other examples of antiproliferative agents with potential chemopreventive efficacy in colon are 2-difluoromethylornithine, dehydroepiandrosterone, and selenium. Differentiating agents such as **retinoids** and deltanoids also may slow proliferation and progression. Antioxidants have potential for interfering with both mutagenicity and proliferation (e.g., by preventing oxidative activation of carcinogens and scavenging activated oxygen species generated during inflammation). The same mechanistic principles apply to identification of dietary chemopreventive intervention for colorectal carcinogenesis. For example, lowering dietary fat and increasing dietary fiber lead to lower colorectal mucosal proliferation, and cruciferous vegetables contain agents such as indoles and dithiolthiones that have shown antimutagenic activity.

L6 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1995:496652 Document No.: PREV199598520202. Genetic and cellular changes in colorectal cancer: Proposed targets of chemopreventive agents. Greenwald, Peter [Reprint author]; Kelloff, Gary J.; Boone, Charles W.; McDonald, Sharon S.. Div. Cancer Prevention Contol, Natl. Cancer Inst., Build. 31, 9000 Rockville, Pike, Bethesda, MD 20892, USA. Cancer Epidemiology

Biomarkers and Prevention, (1995) Vol. 4, No. 7, pp. 671-702.
ISSN: 1055-9965. Language: English.

AB Progress in development of a genetic model for colorectal tumorigenesis and human chemoprevention research may allow the mechanism-based identification of targets and chemopreventive agents that will protect against colorectal cancer. For example, numerous mutagenic events can occur throughout colorectal carcinogenesis, including loss of heterozygosity in tumor suppressor genes such as **APC**, MCC, DCC, and p53, as well as in oncogenes such as K-ras. Chemopreventive agents that inhibit mutagenic activity such as N-acetyl-l-cysteine, oltipraz, and nonsteroidal anti-inflammatory drugs may protect against these mutations. Also, agents such as perillyl alcohol and lovastatin that interfere with protein isoprenylation and, hence, inhibit oncogene activation may protect against aberrant K-ras expression. Hyperproliferation in normal mucosa, leading to early adenomas, and cellular proliferation, leading to growth and progression of neoplasia, are also aspects of colorectal carcinogenesis that can be controlled by chemopreventive agents. Calcium is a chemopreventive agent for which there is both clinical and experimental evidence of inhibition of cell proliferation in colon mucosa. Other examples of and proliferative agents with potential chemopreventive efficacy in colon are 2-difluoromethylornithine, dehydroepiandrosterone, and selenium. Differentiating agents such as **retinoids** and deltanoids also may slow proliferation and progression. Antioxidants have potential for interfering with both mutagenicity and proliferation (e.g., by preventing oxidative activation of carcinogens and scavenging activated oxygen species generated during inflammation). The same mechanistic principles apply to identification of dietary chemopreventive intervention for colorectal carcinogenesis. For example, lowering dietary fat and increasing dietary fiber lead to lower colorectal mucosal proliferation, and cruciferous vegetables contain agents such as indoles and dithiolthiones that have shown antimutagenic activity.

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:19:39 ON
     22 OCT 2003
L1             2 S ANTINGEN PRESENTING CELL
L2         46456 S L1 AND ANTIGEN PRESENTING CELL OR "APC"
L3            27 S L2 AND RETINOIDS
L4             7 S L3 AND CYTOKINE
L5             5 DUP REMOVE L4 (2 DUPLICATES REMOVED)
L6            15 DUP REMOVE L3 (12 DUPLICATES REMOVED)

=> s l2 and "pan-RXR agonist"
L7             0 L2 AND "PAN-RXR AGONIST"

=> s l2 and retinoid receptor agonist
L8             0 L2 AND RETINOID RECEPTOR AGONIST

=> s l2 and agonist
L9           366 L2 AND AGONIST

=> s l9 and RXR receptor
L10            1 L9 AND RXR RECEPTOR

=> d l10 cbib abs

L10  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS on STN
2003:597443   Document No. 139:208228  Adenomatous Polyposis Coli (APC
     )-independent Regulation of .beta.-Catenin Degradation via a Retinoid X
     Receptor-mediated Pathway.  Xiao, Jia-Hao; Ghosn, Corine; Hinchman, Cory;
     Forbes, Chad; Wang, Jenny; Snider, Nonna; Cordrey, Allison; Zhao, Yi;
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Chandraratna, Roshantha A. S. (Departments of Biology and Chemistry, Retinoid Research, Allergan, Inc., Irvine, CA, 92623, USA). Journal of Biological Chemistry, 278(32), 29954-29962 (English) 2003. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB .beta.-Catenin is a component of stable cell adherent complexes whereas its free form functions as a transcription factor that regulate genes involved in oncogenesis and metastasis. Free .beta.-catenin is eliminated by two adenomatous polyposis coli (**APC**)-dependent proteasomal degrdn. pathways regulated by glycogen synthase kinase 3.beta. (GSK3.beta.) or p53-inducible Siah-1. Dysregulation of .beta.-catenin turnover consequent to mutations in crit. genes of the **APC** -dependent pathways is implicated in cancers such as colorectal cancer. We have identified a novel retinoid X receptor (RXR)-mediated **APC** -independent pathway in the regulation of .beta.-catenin. In this proteasomal pathway, RXR **agonists** induce degrdn. of .beta.-catenin and RXR.alpha. and repress .beta.-catenin-mediated transcription. In vivo, .beta.-catenin interacts with RXR.alpha. in the absence of ligand, but RXR **agonists** enhanced the interaction. RXR **agonist** action was not impaired by GSK3.beta. inhibitors or deletion of the GSK3.beta.-targeted sequence from .beta.-catenin. In **APC**- and p53-mutated colorectal cancer cells, RXR **agonists** still inactivated endogenous .beta.-catenin via RXR.alpha.. Interestingly, deletion of the RXR.alpha. A/B region abolished ligand-induced .beta.-catenin degrdn. but not RXR.alpha.-mediated transactivation. RXR.alpha.-mediated inactivation of oncogenic .beta.-catenin paralleled a redn. in cell proliferation. These results suggest a potential role for RXR and its **agonists** in the regulation of .beta.-catenin turnover and related biol. events.

=> s l9 and retinoid receptor
L11 1 L9 AND RETINOID RECEPTOR

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L11 ANSWER 1 OF 1 MEDLINE on STN
2002069855 Document Number: 21653741. PubMed ID: 11795437.
Chemopreventive agents inhibit aberrant proliferation of the aneuploid phenotype in a colon epithelial cell line established from **Apc** 1638N [+/-] mouse. Katdare M; Kopelovich L; Telang N. (Chemoprevention Research Laboratory, Strang Cancer Prevention Center, New York, New York 10021, USA.) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2001 Dec) 952 169-74. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Loss of function of the adenomatous polyposis coli (**APC**) tumor suppressor gene predisposes for familial adenomatous polyposis (FAP) syndrome. The **Apc** gene knockout mice exhibit accelerated intestinal carcinogensis modifiable by diverse pharmacological agents. Present experiments utilized the **Apc**[+/-] 1638N COL colon epithelial cell line (origin: histologically normal colon) as the model. **Retinoid receptor** modulator 9-cis-retinoic acid (9-cis-RA), ornithine decarboxylase inhibitor difluoromethyl ornithine (DFMO), and nonselective cyclooxygenase inhibitor sulindac (SUL) represented the chemopreventive test compounds. Population doubling, cell cycle progression, and anchorage-independent growth provided mechanistic end points for chemopreventive efficacy. Treatment of 1638N COL cells with 9-cis-RA, DFMO and SUL produced a dose-dependent cytostatic growth arrest by decreasing the number of population doublings and altering aneuploid G0/G1:S+G2/M ratio. The clonally expanded 1638N-C11 cells selected for anchorage-independent growth exhibited decreased anchorage-independent colony formation in response to treatment with the three test compounds. Susceptibility of preneoplastic 1638N COL cells to mechanistically distinct chemopreventive agents validates a unique epithelial cell culture model for FAP syndrome, and facilitates

investigations on **Apc** regulated colon carcinogenesis and cancer prevention.

=> s l2 and "SR11237"
L12 0 L2 AND "SR11237"

=> s "SR11237"
L13 105 "SR11237"

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L14 0 L13 AND APC

=> s l13 and retinoid receptor
L15 21 L13 AND RETINOID RECEPTOR

=> s l15 and antigen presenting cell
L16 1 L15 AND ANTIGEN PRESENTING CELL

=> d l16 cbib abs

L16 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
2001:780660 Document No. 135:327340 Retinoid compositions and methods for use in modulating immune system function. Geissmann, Frederic; Lepelletier, Yves; Dy, Michel; Durandy, Anne; Revy, Patrick; Chambon, Pierre (Fr.). PCT Int. Appl. WO 2001078700 A2 20011025, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-IB484 20010412. PRIORITY: US 2000-PV196921 20000413.
AB Vitamin A (retinol) deficiency results in impaired response to infection and increased mortality. The inventors show that retinol activates immature dendritic cells (DC) and enhances antigen presentation via a cross-talk with inflammatory cytokines, whereas it increases DC death in the absence of these cytokines. These effects, that are mediated through retinoic acids and distinct nuclear **retinoid receptor** pathways, can be dissocd. from each other with selective synthetic retinoids. The invention identifies a novel cellular target and function for retinoids, provides compns. and methods for modulating the immune system and for treating or preventing various phys. disorders in animals, preferably via controlling activation and/or apoptosis in **antigen -presenting cells** using selective retinoids.

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L17 17 DUP REMOVE L15 (4 DUPLICATES REMOVED)

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L17 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
2002:298802 Document No. 136:305480 Nicotine modulates the effects of retinoids on growth inhibition and RAR.beta. expression in lung cancer cells. Chen, Guo-quan; Lin, Bingzhen; Dawson, Marcia I.; Zhang, Xiao-kun (Cancer Center, The Burnham Institute, La Jolla, CA, 92037, USA). International Journal of Cancer, 99(2), 171-178 (English) 2002. CODEN: IJCNAW. ISSN: 0020-7136. Publisher: Wiley-Liss, Inc..
AB Epidemiol. and animal studies have demonstrated that vitamin A and its natural and synthetic derivs., retinoids, are effective agents in preventing the development of tobacco-assocd. cancers. Unfortunately,

clin. trials of retinoids on cigarette smokers have shown lack of efficacy in preventing lung cancer. In this study, the authors investigated the effect of nicotine on the anti-cancer activity of all trans-retinoic acid (trans-RA) in human lung cancer cells. These results demonstrated that nicotine could abrogate the growth inhibitory effect of trans-RA by suppressing its ability to induce the expression of RA receptor beta (RAR.beta.), a tumor suppressor. The inhibitory effect of nicotine was accompanied with induction of orphan receptor TR3. Inhibition of TR3 expression by over-expression of TR3 anti-sense RNA in H460 lung cancer cells strongly prevented the suppressive effect of nicotine on trans-RA activity. Treatment with nicotine or the cotransfection of TR3 expression vector inhibited the induction of RAR.beta. promoter activity by trans-RA in transient transfection assays. The inhibition of RAR.beta. promoter activity was due to the interaction of TR3 with orphan receptor COUP-TF, resulting in inhibition of COUP-TF DNA binding and transactivation on the RAR.beta. promoter. Furthermore, the authors found that nicotine failed to suppress the effect of a retinoid X receptor (RXR)-selective retinoid **SR11237** on inducing both growth inhibition and RAR.beta. promoter activity, due to the ability of **SR11237** to activate the RAR.beta. promoter through the RXR/TR3 heterodimer. Together, these results demonstrate that nicotine suppresses the growth inhibitory effects of trans-RA by inhibiting RAR.beta. expression through its induction of TR3 expression and suggest that RXR-selective retinoids may be more effective than classical retinoids for preventing and treating tobacco-assocd. cancers.

L17 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

2001:780660 Document No. 135:327340 Retinoid compositions and methods for use in modulating immune system function. Geissmann, Frederic; Lepelletier, Yves; Dy, Michel; Durandy, Anne; Revy, Patrick; Chambon, Pierre (Fr.). PCT Int. Appl. WO 2001078700 A2 20011025, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-IB484 20010412. PRIORITY: US 2000-PV196921 20000413.

AB Vitamin A (retinol) deficiency results in impaired response to infection and increased mortality. The inventors show that retinol activates immature dendritic cells (DC) and enhances antigen presentation via a cross-talk with inflammatory cytokines, whereas it increases DC death in the absence of these cytokines. These effects, that are mediated through retinoic acids and distinct nuclear **retinoid receptor** pathways, can be dissocd. from each other with selective synthetic retinoids. The invention identifies a novel cellular target and function for retinoids, provides compns. and methods for modulating the immune system and for treating or preventing various phys. disorders in animals, preferably via controlling activation and/or apoptosis in antigen-presenting cells using selective retinoids.

L17 ANSWER 3 OF 17 MEDLINE on STN DUPLICATE 1

1999107209 Document Number: 99107209. PubMed ID: 9892191. Retinoic acid increases tyrosine phosphorylation of focal adhesion kinase and paxillin in MCF-7 human breast cancer cells. Zhu W Y; Jones C S; Amin S; Matsukuma K; Haque M; Vuligonda V; Chandraratna R A; De Luca L M. (Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892-4255, USA.) CANCER RESEARCH, (1999 Jan 1) 59 (1) 85-90. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Treatment of estrogen receptor (ER)-positive MCF-7 human breast cancer cells with retinoic acid (RA) inhibited cell growth and increased cell adhesion to fibronectin. In contrast, ER- MDA-MB-231 cells failed to

respond. Western blot analysis showed that tyrosine phosphorylation of two major bands at Mr 125,000 and Mr 68,000 was induced by RA in ER+ MCF-7 human breast carcinoma cells. However, this induction was a late phenomenon detectable at 12 and 24 h, but not within 3 h. A similar increase of tyrosine phosphorylation by RA was observed in ER+ human breast cancer cell lines T-47D and ZR-75-1, but not in the ER- cell lines MDA-MB-231, MDA-MB-453, and MDA-MB-468. Focal adhesion kinase and paxillin, which localize in focal adhesion plaques and may play important roles in the integrin signaling pathway, were identified as the major proteins showing RA-induced tyrosine phosphorylation. The retinoid X receptor-selective compound **SR11237** failed to induce tyrosine phosphorylation, indicating that retinoid X receptor activation is not involved in this phenomenon. In contrast, stable overexpression of a truncated RA receptor (RAR) alpha cDNA, RARalpha403, with strong RAR dominant negative activity prevented the increase in tyrosine phosphate, suggesting that RAR signaling is involved in RA-induced tyrosine phosphorylation. Tyrosine phosphorylation was induced the most by the RAR-alpha (193836), followed by RAR-gamma (194433), but was not significantly induced by RAR-gamma (193174)-selective retinoids. This study demonstrates a coordinated albeit relatively late effect of RA on cell adhesion and tyrosine phosphorylation in ER+ human breast cancer cells and suggests RAR-alpha as the major responsible **retinoid receptor**.

L17 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
1998:84496 Document No. 128:239545 Effects of conformationally restricted synthetic retinoids on ovarian tumor cell growth. Wu, Shujian; Zhang, Dongmei; Donigan, Anne; Dawson, Marcia I.; Soprano, Dianne Robert; Soprano, Kenneth J. (Department of Microbiology and Immunology, Temple University School of Medicine, Philadelphia, PA, 19140, USA). Journal of Cellular Biochemistry, 68(3), 378-388 (English) 1998. CODEN: JCEBD5. ISSN: 0730-2312. Publisher: Wiley-Liss, Inc..
AB Conformationally restricted retinoids have been used to investigate the role of individual RAR subtypes and RXR in mediating the growth response of ovarian tumor cells to retinoids. The results show that treatment of all-trans-RA-sensitive CAOV-3 cells with retinoids that bind and activate a single RAR or RXR led to a partial inhibition of growth. Treatment of all-trans-RA- resistant SKOV-3 cells did not alter growth. Max. inhibition of growth, comparable to that obsd. following treatment with natural retinoids such as all-trans-RA and 9-cis-RA, was obtained only following treatment with a combination of an RAR-selective compd. and an RXR-selective one. These results suggest that activation of both RAR and RXR classes is required to obtain max. inhibition of ovarian tumor cell growth by retinoids. In addn., one compd., AHPN, was found to inhibit both RA-sensitive CAOV-3 and RA-resistant SKOV-3 cells. Further study of the effects of this retinoid showed that AHPN acts through an apoptotic pathway. Taken together, the results suggest that retinoids may serve as effective anti-proliferative agents in the treatment of ovarian cancer.

L17 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN
1997:700819 Document No. 128:30107 Inhibition of trans-retinoic acid-resistant human breast cancer cell growth by retinoid X receptor-selective retinoids. Wu, Qiao; Dawson, Marcia I.; Zheng, Yun; Hobbs, Peter D.; Agadir, Anissa; Jong, Ling; Li, Yin; Liu, Ru; Lin, Bingzhen; Zhang, Xiao-Kun (La Jolla Cancer Res. Cent., Burnham Inst., La Jolla, CA, 92037, USA). Molecular and Cellular Biology, 17(11), 6598-6608 (English) 1997. CODEN: MCEBD4. ISSN: 0270-7306. Publisher: American Society for Microbiology.
AB All-trans-retinoic acid (trans-RA) and other retinoids exert anticancer effects through two types of **retinoid receptors**, the RA receptors (RARs) and retinoid X receptors (RXRs). Previous studies demonstrated that the growth-inhibitory effects of trans-RA and related retinoids are impaired in certain estrogen-independent breast cancer cell lines due to their lower levels of RAR.alpha. and RAR.beta.. In this study, we evaluated several synthetic retinoids for their ability to

induce growth inhibition and apoptosis in both trans-RA-sensitive and trans-RA-resistant breast cancer cell lines. Our results demonstrate that RXR-selective retinoids, particularly in combination with RAR-selective retinoids, could significantly induce RAR.beta. and inhibit the growth and induce the apoptosis of trans-RA-resistant, RAR.alpha.-deficient MDA-MB-231 cells but had low activity against trans-RA-sensitive ZR-75-1 cells that express high levels of RAR.alpha.. Using gel retardation and transient transfection assays, we found that the effects of RXR-selective retinoids on MDA-MB-231 cells were most likely mediated by RXR-nur77 heterodimers that bound to the RA response element in the RAR.beta. promoter and activated the RAR.beta. promoter in response to RXR-selective retinoids. In contrast, growth inhibition by RAR-selective retinoids in trans-RA-sensitive, RAR.alpha.-expressing cells most probably occurred through RXR-RAR.alpha. heterodimers that also bound to and activated the RAR.beta. promoter. In MDA-MB-231 clones stably expressing RAR.alpha., both RAR.beta. induction and growth inhibition by RXR-selective retinoids were suppressed, while the effects of RAR-selective retinoids were enhanced. Together, our results demonstrate that activation of RXR can inhibit the growth of trans-RA-resistant MDA-MB-231 breast cancer cells and suggest that low cellular RAR.alpha. may regulate the signaling switch from RAR-mediated to RXR-mediated growth inhibition in breast cancer cells.

L17 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1997:68308 Document No. 126:169567 Retinoid X receptor (RXR) within the RXR-retinoic acid receptor heterodimer binds its ligand and enhances retinoid-dependent gene expression. Minucci, Saverio; Leid, Mark; Toyama, Reiko; Saint-Jeannet, Jean-Pierre; Peterson, Valerie J.; Horn, Valerie; Ishmael, Jane E.; Bhattacharyya, Nisan; Dey, Anup; Dawid, Igor B.; Ozato, Keiko (Lab. Mol. Growth Regulation, Natl. Inst. Health, Bethesda, MD, 20892, USA). Molecular and Cellular Biology, 17(2), 644-655 (English) 1997. CODEN: MCEBD4. ISSN: 0270-7306. Publisher: American Society for Microbiology.

AB Retinoic acid receptor (RAR) and retinoid X receptor (RXR) form heterodimers and regulate retinoid-mediated gene expression. We studied binding of RXR- and RAR-selective ligands to the RXR-RAR heterodimer and subsequent transcription. In limited proteolysis analyses, both RXR and RAR in the heterodimer bound their resp. ligands and underwent a conformational change in the presence of a retinoic acid-responsive element. In reporter analyses, the RAR ligand (but not the RXR ligand), when added singly, activated transcription, but coaddn. of the two ligands led to synergistic activation of transcription. This activation required the AF-2 domain of both RXR and RAR. Genomic footprinting anal. was performed with P19 embryonal carcinoma cells, in which transcription of the RAR.beta. gene is induced upon retinoid addn. Paralleling the reporter activation data, only the RAR ligand induced in vivo occupancy of the RAR.beta.2 promoter when added singly. However, at suboptimal concns. of RAR ligand, coaddn. of the RXR ligand increased the stability of promoter occupancy. Thus, liganded RXR and RAR both participate in transcription. Finally, when these ligands were tested for teratogenic effects on zebra fish and Xenopus embryos, we found that coadministration of the RXR and RAR ligands caused more severe abnormalities in these embryos than either ligand alone, providing biol. support for the synergistic action of the two ligands.

L17 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1997:530441 Document No. 127:215160 Receptor specificity of retinoid-induced epidermal hyperplasia: effect of RXR-selective agonists and correlation with topical irritation. Thacher, Scott M.; Standeven, Andrew M.; Athanikar, Jyothi; Kopper, Scott; Castilleja, Oliver; Escobar, Maria; Beard, Richard L.; Chandraratna, Roshantha A. S. (Retinoid Research, Department of Biology, Irvine, CA, USA). Journal of Pharmacology and Experimental Therapeutics, 282(2), 528-534 (English) 1997. CODEN: JPETAB. ISSN: 0022-3565. Publisher: Williams & Wilkins.

AB Retinoid induction of epidermal hyperplasia was investigated in hairless

mice with synthetic ligands for the retinoic acid (RAR) and retinoid X (RXR) nuclear receptors. Induction of hyperplasia by all-trans retinoic acid and the RAR-specific retinoids TTNPB, tazarotene and AGN 190121 varied over a wide range (ED50 = 0.2-100 nmol/animal in three daily applications). Potency of induction was not directly correlated to receptor-binding affinity, but specificity of action could be demonstrated by inhibition with the high-affinity antagonist of the RARs, AGN 193109. Although RAR is functionally complexed with RXR in vivo, RXR-selective compds. have only weak potency in induction of hyperplasia. The ED50 value of the RXR-selective AGN 191701 was 600 nmol/animal compared with an ED50 value of 0.2 nmol for the structurally similar RAR-selective TTNPB. **SR11237** and SR11217, also RXR-selective, each have an ED50 value of >1000 nmol. Unlike RAR-specific retinoids, RXR-selective retinoids cause only very mild skin flaking at high doses. Relative potencies for cumulative topical irritation (flaking and abrasion) of both RAR and RXR ligands were well correlated with epidermal hyperplasia. These data are consistent with RXR as a silent partner in the RAR-RXR heterodimer in skin.

L17 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:577830 Document No. 125:266583 Compounds affecting RXR homodimer formation and DNA binding and reporter gene assays for their identification. Pfahl, Magnus; Zhang, Xiao-kun; Lehmann, Juergen M.; Dawson, Marcia I.; Cameron, James F.; Hobbs, Peter D.; Jong, Ling (La Jolla Cancer Research Foundation, USA). U.S. US 5552271 A 19960903, 26 pp., Cont.-in-part of U.S. Ser. No. 901,719, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1992-982174 19921125. PRIORITY: US 1992-901719 19920616.

AB Reporter gene and electrophoretic mobility shift assay methods of screening substances for their ability to affect the formation of a retinoid X receptor homodimer by measuring the rate of dimer formation upon exposure to the substance is described. These methods can also be used to test a substance for an effect on a retinoid X receptor homodimer's ability to bind DNA using a thyroid hormone-responsive element. A method of inhibiting retinoid X receptor heterodimer formation, e.g. with RAR, by increasing the formation of the receptor homodimer is also described. A method of inhibiting an activity of a retinoid X receptor homodimer is also provided. In addn., a method of screening a response element for binding with a retinoid X receptor homodimer is provided. Finally, the invention provides methods of activating retinoid X receptor homodimer formation. The assays demonstrate that homo- and heterodimerization of RXR represent distinct transcriptional regulatory mechanisms and that RXR acts as an auxiliary receptor for retinoic acid, thyroid hormone, and vitamin D receptors.

L17 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:175406 Document No. 124:278261 Retinoic acid down-regulation of fibronectin and retinoic acid receptor .alpha. proteins in NIH-3T3 cells. Block of this response by ras transformation. Scita, Giorgio; Darwiche, Nadine; Greenwald, Eileen; Rosenberg, Miriam; Politi, Katerina; De Luca, Luigi M. (Lab. Cell. Carcinog. Tumor Promotion, Natl Inst. Health, Bethesda, MD, 20892, USA). Journal of Biological Chemistry, 271(11), 6502-8 (English) 1996. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB All-trans-retinoic acid (RA) markedly reduced the level of intracellular fibronectin (FN) in a time- and concn.-dependent fashion in NIH-3T3 cells, but not in NIH-3T3 cells transformed by an activated Ha-ras oncogene. Pulse/chase expts. indicated that RA affects FN biosynthesis rather than its turnover rate. Steady state levels of FN transcripts did not change after treatment of the cells with RA for various times or concns., suggesting that RA acts at the translational level. Similar effects were obsd. in other fibroblasts. In NIH=3T3 cells, RA had distinct effects on different receptors; it down-modulated retinoic acid receptor (RAR) .alpha. protein and transcript levels, it up-regulated RAR.beta. transcripts, and it had no effect on RAR.gamma.. Transformation of

NIH-3T3 cells with an activated Ha-ras oncogene down-modulated RAR expression and abolished responsiveness to RA. We identified the retinoid signal transduction pathways responsible for the effects of RA on FN and RAR.alpha. proteins by the use of the retinoid X receptor-selective compd., **SR11237**, by stable over-expression of a truncated form of the RAR.alpha. gene, RAR.alpha.403, with strong RAR dominant neg. activity, and by overexpression of RAR.alpha.. We conclude that: (1) RA-dependent FN down-modulation is mediated by RARs, (2) retinoid X receptors mediate the obsd. redn. of RAR.alpha. by RA,m and (3) the block of RA responsiveness in Ha-ras cells cannot be overcome by overexpression of RAR.alpha.. These studies have defined fibronectin and RAR.alpha. as targets of RA in fibroblast cells and have shown that oncogenic transformation renders the cells resistant to RA action.

L17 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:238710 Document No. 124:332032 Retinoid X receptor-specific retinoids inhibit the ability of retinoic acid receptor-specific retinoids to increase the level of insulin-like growth factor binding protein-3 in human ectocervical epithelial cells. Hembree, Joan R.; Agarwal, Chapla; Beard, Richard L.; Chandraratna, Roshantha A. S.; Eckert, Richard L. (Department Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH, 44106-4970, USA). Cancer Research, 56(8), 1794-9 (English) 1996. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB The hormones derived from vitamin a and related synthetic ligands (retinoids) are important regulators of differentiation and development and have been shown to be therapeutically useful in the treatment of cervical cancer. All-trans-retinoic acid exerts its effects by activation of retinoic acid receptor (RAR) and retinoid X receptor (RXR) heterodimers. These heterodimers bind to the retinoic acid response elements of target genes to regulate gene expression. RXR ligands act through RXR homodimers to regulate gene expression. In the present study, we describe the effects of RAR- and RXR-specific ligands on the regulation of insulin-like growth factor binding protein-3 (IGFBP-3) prodn. and cell proliferation in human ectocervical epithelial (ECE) cell lines. Treatment of ECE16-1 cells with a RAR-specific ligand (TTNPB) or a ligand that interacts with both RAR and RXR receptors (9-cis-retinoic acid) increases IGFBP-3 levels and suppresses cell proliferation. In contrast, RXR-specific ligands (AGN191701, SR11217, and **SR11237**) do not regulate proliferation and slightly suppress the IGFBP-3 level. Cotreatment with increasing concns. (0.01-1000 nm) of RXR-specific ligand antagonizes the growth suppressive and IGFBP-3 increasing effects of 1000 nM TTNPB. Similar results are obsd. in two other ECE cell lines, ECE16-D1 and ECE16-D2. These results indicate that RXR-specific ligands can antagonize RAR responses in these cell lines and suggest that a RAR-specific retinoid may be superior to one with mixed RAR/RXR binding activity for inhibiting cervical cancer cell proliferation. Moreover, the antagonism of RAR-dependent responses by RXR-specific ligands is consistent with a squelching model in which the RXR-specific ligand drives formation of RXR/RXR homodimers at the expense of the more active RAR/RXR heterodimers.

L17 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:203534 Document No. 124:306673 Potential role for retinoic acid receptor-.gamma. in the inhibition of breast cancer cells by selective retinoids and interferons. Fanjul, Andrea N.; Bouterfa, Hakim; Dawson, Marcia; Pfahl, Magnus (Sidney Kimmel Cancer Center, La Jolla, CA, 90237, USA). Cancer Research, 56(7), 1571-7 (English) 1996. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Retinoids are known to inhibit the growth of a wide variety of cancer cells, including breast cancer cells. Advances made in recent years in the understanding of the mol. mechanisms of retinoid action have allowed the design of retinoids with selective activities. Such selective retinoids are of particular interest, because they may reduce the no. of undesirable side effects obsd. with natural compds. Here, the authors

have compared the growth-inhibitory activities of natural retinoids with various selective retinoids, including anti-activator protein (AP)-1 selective compds. on estrogen receptor-pos. and -neg. breast cancer cell lines. In addn., the authors have investigated cooperativity between selective retinoids and interferons (IFNs) and have begun to analyze the pathways that these two different growth inhibitors use for antagonizing breast cancer cell proliferation. The authors obsd. that several selective retinoids can inhibit breast cancer cells as efficiently as the natural compds. Anti-AP-1-selective retinoids are as effective as retinoic acid receptor (RAR)-.beta./.gamma.-selective compds. This lets the authors conclude that retinoid-induced inhibition of breast cancer cell growth does not require **retinoid receptor** transactivation. Several synthetic retinoids including anti-AP-1-selective compds. show synergism with IFNs. However, true synergism between the two different types of growth regulators was seen only when both classes of mols. were used at low concns. RAR-.beta./.gamma. and anti-AP-1 selective retinoids, but not RAR-.alpha.-selective compds., induced increased RAR-.gamma. mRNA levels. Interestingly, IFNs at elevated concns. (100 units/mL and higher) also induced increased RAR-.gamma. expression. Thus, when used at high concns., IFNs may activate growth-inhibitory pathways overlapping with those activated by retinoids. Because increased RAR-.gamma. expression is induced by the two different classes of breast cancer cell inhibitors, it is likely to have an important role in controlling the growth of these cancer cells.

L17 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:461449 Document No. 125:185042 RAR and RXR selective ligands cooperatively induce apoptosis and neuronal differentiation in P19 embryonal carcinoma cells. Horn, Valerie; Minucci, Saverio; Ogryzko, Vasily V.; Adamson, Eileen D.; Howard, Bruce H.; Levin, Arthur A.; Ozato, Keiko (Natl. Institute Child Health and Human Development, Natl. Institutes Health, Bethesda, MD, 20892, USA). FASEB Journal, 10(9), 1071-1077 (English) 1996. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.

AB Retinoids cause differentiation in embryonal carcinoma (EC) cells, thus mimicking events in mammalian development. Here, we show that retinoids also cause apoptosis in P19 EC cells. Characteristic DNA fragmentation was obsd. within 36 h after addn. of retinoic acid (RA). Synthetic retinoids that are selective for RA receptors (RAR) were also effective in inducing apoptosis, whereas RXR selective ligands were without effect. The combination of RAR and RXR ligands resulted in a synergistic increase in apoptotic cell death. As with apoptosis, neuronal differentiation of P19 cells was synergistically induced by the combination of RAR and RXR ligands. Data obtained with an RAR antagonist and with P19 cells carrying a dominant neg. RXR indicate that the two processes are receptor mediated. Together, our results indicate that retinoid-induced apoptosis and neuronal differentiation are closely coupled, and that both RAR and RXR play a role in these processes as active receptors for their resp. ligands.

L17 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1996:22013 Document No. 124:166072 Myeloid differentiation and retinoblastoma phosphorylation changes in HL-60 cells induced by retinoic acid receptor- and retinoid X receptor-selective retinoic acid analogs. Brooks, S. Caroll, III; Kazmer, Sonja; Levin, Arthur A.; Yen, Andrew (Dep. of Pathology, Cornell Univ., Ithaca, NY, USA). Blood, 87(1), 227-37 (English) 1996. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: Saunders.

AB The ability of subtypes of retinoic acid receptors (RARs) and retinoid X receptors (RXRs) singly and in combination to elicit myeloid differentiation, G1/0-specific growth arrest, and retinoblastoma (RB) tumor suppressor protein dephosphorylation was detd. in the human myeloblastic leukemia cell line HL-60 using subtype-selective retinoic acid (RA) analogs. RA analogs that selectively bind only to RARs (Am580 and/or TTNPB) or to RXRs (Ro 25-6603, **SR11237**, and/or SR11234)

did not elicit the above-mentioned three cellular responses. In contrast, simultaneous treatment with both an RAR-selective ligand (Am580 or TTNPB) and an RXR-selective ligand (Ro 25-6603, **SR11237**, or SR11234) induced all three cellular processes. An RAR.alpha.-selective ligand used with an RXR-selective ligand generated the same responses as did all-trans RA or 9-cis RA, which affect both families of receptors, suggesting an important role for RAR.alpha. among RAR subtypes in eliciting cellular response. Consistent with this finding, the RAR.alpha. antagonist, Ro 41-5253, reduced the level of the cellular responses elicited by treatment with an RAR.alpha.-selective ligand plus RXR-selective ligand. The coupling of the shift of RB to its hypophosphorylated form with G1/0 arrest and differentiation in response to ligands is consistent with a possible role of RB as a downstream target or effector of RAR.alpha. and RXR in combination.

L17 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1995:372259 Document No. 122:123934 Endogenous retinoic acid receptor (RAR)-retinoid X receptor (RXR) heterodimers are the major functional forms regulating retinoid-responsive elements in adult human keratinocytes. Binding of ligands to RAR only is sufficient for RAR.cntdot.RXR heterodimers to confer ligand-dependent activation of hRAR.beta.2/RARE (DR5). Xiao, Jia-Hao; Durand, Beatrice; Chambon, Pierre; Voorhees, John J. (Department of Dermatology, University of Michigan, Ann Arbor, MI, 48109, USA). Journal of Biological Chemistry, 270(7), 3001-11 (English) 1995. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

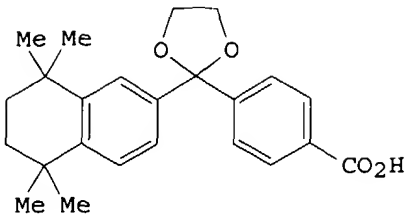
AB The authors have examd. how retinoic acid receptors (RARs) and retinoid X receptors (RXRs) at physiol. concns. regulate distinct retinoid-responsive elements, hRAR.beta.2/.beta.RARE (DR5) and rCRBPII/RXRE (DR1), in keratinocytes from human skin, a major retinoid target. In vitro, endogenous RAR.gamma. and RXRs bound to these elements as heterodimers (RAR.cntdot.RXR) but not homodimers (RAR.cntdot.RAR or RXR.cntdot.RXR). In cultured keratinocytes, all-trans retinoic acid, 9-cis retinoic acid, and CD 367 activated .beta.RARE but not RXRE via endogenous RAR.cntdot.RXR (ED50 = 2.3, 3.8, and 0.3 nM, resp.) whereas **SR11237** showed no significant effect. All-trans retinoic acid, 9-cis retinoic acid, and SR 11237 activated RXRE via overexpressed RXR.cntdot.RXR (Ed50 = 110, 120, and 11 nM, resp.), indicating interconversion between retinoic acid isomers, whereas co-overexpression of RAR.alpha. or RAR.gamma. suppressed this activation. Unlike 9-cis retinoic acid, CD 367 neither induced formation of nor activated RXR.cntdot.RXR. Overexpression of RAR or RXR mutated in transactivation domain AF-2 suppressed endogenous receptor activity over .beta.RARE. The data suggest that (1) in keratinocytes, RAR.cntdot.RXR-mediated pathway dominates over that mediated by RXR.cntdot.RXR; (2) RAR-selective CD 367 and RXR-selective **SR11237** can be used to identify these two distinct pathways, resp.; (3) .beta.RARE is mainly regulated by RAR.cntdot.RXR, in which RAR alone confers ligand inducibility whereas AF-2 of unliganded RXR is required for transactivation by liganded RAR AF-2; (4) lack of RXRE activity in keratinocytes is due to low endogenous levels of RXR.cntdot.RXR and inhibition by RAR.cntdot.RXR; and (5) interaction among RXRs is much lower than that between RAR and RXR.

L17 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1994:526151 Document No. 121:126151 RXR receptor homodimer formation and bridged bicyclic aromatic compounds and their use in modulating gene expression and screening modulating compounds. Pfahl, Magnus; Zhang, Xiao Kun; Lehmann, Jurgen M.; Dawson, Marcia I.; Camerion, James F.; Hobbs, Peter D.; Jong, Ling (La Jolla Cancer Research Foundation, USA; SRI International). PCT Int. Appl. WO 9412880 A2 19940609, 102 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US11492 19931124.

PRIORITY: US 1992-982305 19921125; US 1992-982174 19921125.

GI



I

AB The invention provides a method of screening a substance for the ability to affect the formation of a retinoid X receptor (RXR) homodimer comprising combining the substance and a soln. contg. RXR receptors and detg. the presence of homodimer formation. The screening method can be used to det. compds. which selectively activate homodimer formation and heterodimer formation. Also provided is a method of screening a substance for an effect on a RXR receptor homodimer's ability to bind DNA comprising combining the substance with the homodimer and detg. the effect of the compd. on the homodimer's ability to bind DNA. Finally, the invention provides methods of activating RXR receptor homodimer formation. Bridged bicyclic arom. compds. are provided. These compds. are useful for modulating gene expression of retinoic acid receptors, vitamin D receptors and thyroid receptors. Pharmaceutical compns. and methods for modulating gene expression are provided as well. Retinoids were identified that specifically induce RXR homodimer formation and activate RXR homodimers on specific genetic response elements but not RAR/RXR heterodimers. These retinoids allow the specific activation of RXR-selective response pathways, while not inducing RAR-dependent response pathways. One of these compds., **SR11237** (I), was prepd. from Me 4-[(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthalenyl)carbonyl]benzoate (prepn. given).

L17 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2003 ACS on STN

1994:672953 Document No. 121:272953 Endogenous retinoid X receptors can function as hormone receptors in pituitary cells. Davis, Kelly D.; Berrodin, Thomas J.; Stelmach, John E.; Winkler, Jeffrey D.; Lazar, Mitchell A. (Dep. Med. Genet. Chem., Univ. Pennsylvania, Philadelphia, PA, 19104, USA). Molecular and Cellular Biology, 14(11), 7105-10 (English) 1994. CODEN: MCEBD4. ISSN: 0270-7306. Publisher: American Society for Microbiology.

AB Retinoids regulate gene transcription by interacting with both retinoic acid (RA) receptors (RARs) and retinoid X receptors (RXRs). Since unliganded RXRs can act as heterodimerization partners for RARs and other nuclear hormone receptors, it is unclear whether ligand binding by RXRs actually regulates the expression of naturally occurring genes. To address this issue, the authors synthesized the RXR-selective retinoid **SR11237** and confirmed its specificity in transient transfection and proteolytic susceptibility assays before using it to assess the contribution of ligand-activated RXRs to retinoid action. Unlike RAR ligands, **SR11237** did not increase endogenous RAR.beta. mRNA levels in F9 embryonal carcinoma cells, even though it activated transcription of an RXR-responsive reporter gene in these cells. Thus, it is likely that RARs mediate the induction of RAR.beta. gene expression by RA. In contrast, the RXR-specific ligand induced rat growth hormone mRNA in GH3 pituitary cells, indicating that the effects of RA on growth hormone gene expression at least in part involve ligand binding to endogenous RXRs in vivo. The results indicate that in addn. to serving as cofactors for other nuclear hormone receptors, endogenous RXRs can function as ligand-dependent regulators of gene expression, i.e., classical nuclear hormone receptors.

L17 ANSWER 17 OF 17 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN DUPLICATE 2
94:285590 The Genuine Article (R) Number: NJ884. A PLEIOTROPIC RESPONSE IS INDUCED IN F9 EMBRYONAL CARCINOMA-CELLS AND RHINO MOUSE SKIN BY ALL-TRANS-RETINOIC ACID, A RAR AGONIST BUT NOT BY **SR11237**, A RXR-SELECTIVE AGONIST. GENDIMENICO G J; STIM T B; CORBO M; JANSSEN B; MEZICK J A (Reprint). RW JOHNSON PHARMACEUT RES INST, 1000 US ROUTE 202 S, RARITAN, NJ, 08869 (Reprint); RW JOHNSON PHARMACEUT RES INST, RARITAN, NJ, 08869; BASF AG, W-6700 LUDWIGSHAFEN, GERMANY. JOURNAL OF INVESTIGATIVE DERMATOLOGY (MAY 1994) Vol. 102, No. 5, pp. 676-680. ISSN: 0022-202X. Pub. country: USA; GERMANY. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We evaluated **SR11237**, a retinoid X receptor (RXR)-specific compound, for its pharmacologic effects on cell differentiation in F9 embryonal carcinoma cells and rhino mouse epidermis. **SR11237** can cause RXR/RXR homodimers to form and transactivate a reporter gene containing a RXR-response element. We confirmed, using nuclear receptor co-transfection assays in COS-1 cells, that **SR11237** is effective at transactivating a chloramphenicol acetyltransferase reporter gene through RXRs but not retinoic acid receptors. When **SR11237** was tested for its ability to modulate cell differentiation, it was inactive on F9 embryonal carcinoma cells and rhino mouse skin. Because differentiation in these systems is known to be regulated by RAR-specific compounds, such as all-trans-retinoic acid and (E)-4-[2(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl benzoic acid], our results with **SR11237** are compatible with the concept that classical retinoid pleiotropic responses are mediated by RXR/RAR heterodimeric nuclear receptors rather than through RXR/RXR homodimers.

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=> s langerhans cell
L18      32857 LANGERHANS CELL

=> s l18 and vitamin D
L19         55 L18 AND VITAMIN D

=> s l19 and cytokine
L20         10 L19 AND CYTOKINE

=> dup remove l20
PROCESSING COMPLETED FOR L20
L21          7 DUP REMOVE L20 (3 DUPLICATES REMOVED)

=> d l21 1-7 cbib abs

L21 ANSWER 1 OF 7 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.
    on STN
2000234851 EMBASE The cutaneous citadel: A holistic view of skin and
    immunity. Spellberg B.. Dr. B. Spellberg, 1201 South Catalina Ave. 12,
    Redondo Beach, CA 90277, United States. BJS@humc.edu. Life Sciences 67/5
    (477-502) 23 Jun 2000.
    Refs: 264.
    ISSN: 0024-3205. CODEN: LIFSAK.
    Publisher Ident.: S 0024-3205(00)00653-6. Pub. Country: United States.
    Language: English. Summary Language: English.
AB  Human skin has 4 major functions: endogenous homeostasis (e.g. regulation
    of body temperature and fluid balance), metabolism (e.g. Vitamin
    D synthesis), sensory input, and to serve as a barrier to external
    threats (e.g. infection, mechanical injury, ultraviolet light). It is the
    latter function which concerns this review, for the skin's remarkable
    success in protecting the human body from the outside world is a major
    component of our immune system. The eminent pathologist, Virchow, whose
    work in the mid 19th century revolutionized many aspects of medical
    understanding, viewed the skin as an effective but inanimate barrier (1).
    However, recent technologies have elucidated a highly complex, dynamic
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interplay between the skin and other members of the immune system. (C) 2000 Elsevier Science Inc.

L21 ANSWER 2 OF 7 MEDLINE on STN
2000084977 Document Number: 20084977. PubMed ID: 10617914. Regulatory effects of 1alpha,25-dihydroxyvitamin D(3) on **cytokine** production by human corneal epithelial cells. Suzuki T; Sano Y; Sotozono C; Kinoshita S. (Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.. tsuzuki@ophth.kpu-m.ac.jp) . CURRENT EYE RESEARCH, (2000 Feb) 20 (2) 127-30. Journal code: 8104312. ISSN: 0271-3683. Pub. country: ENGLAND: United Kingdom. Language: English.
AB PURPOSE: The topical administration of 1alpha,25-dihydroxy-**vitamin D**(3) [1alpha,25(OH)(2)D(3)] inhibits **Langerhans cell** (LC) migration and corneal neovascularization in mice. Since the **cytokines** that induce LC migration [e.g. interleukin-1 (IL-1)] and corneal neovascularization [e.g. interleukin-8 (IL-8)] are produced by human corneal epithelial cells, we investigated the inhibitory effects of 1alpha,25(OH)(2)D(3) on **cytokine** production by these cells in vitro. METHODS: In this experiment, human corneal epithelial cells, cultured in DMEM-FBS until confluence, were then switched to serum-free DMEM containing insulin, transferrin, and sodium selenite (DMEM-ITS) for 48 hours. Next, they were cultured with DMEM-ITS containing 1alpha,25(OH)(2)D(3) at concentrations of 10(-7) M, 10(-11) M, or 10(-15) M, and vehicle only (0.1% ethanol). After 6 or 12 hours in this culture, the supernatants were collected and concentrations of IL-1alpha, IL-1b, and IL-8 were quantified by ELISA. RESULTS: Significantly lower levels of IL-1alpha and IL-1b were detected in supernatants from cells cultured with 1alpha, 25(OH)(2)D(3) (10(-7) M, 10(-11) M, and 10(-15) M), compared to cells cultured with vehicle only. This was true at 6 and 12 hours after the addition of 1alpha,25(OH)(2)D(3) ($p < 0.05$). IL-8 production inhibition by 1alpha,25(OH)(2)D(3), on the other hand, was detected at 6 hours ($p < 0.0005$) but not at 12 hours ($p > 0.1$). CONCLUSIONS: 1alpha,25(OH)(2)D(3) inhibits **cytokine** (IL-1alpha, IL-1b, and IL-8) production by human corneal epithelial cells in vitro. We suspect that 1alpha,25(OH)(2)D(3) can inhibit LC migration and corneal neovascularization, as is seen in ocular surface inflammation.

L21 ANSWER 3 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
1999:922802 The Genuine Article (R) Number: 259DL. The effects of dexamethasone, cyclosporine, and **vitamin D**-3 on the activation of dendritic cells stimulated by haptens. Singh S; Aiba S (Reprint); Manome H; Tagami H. TOHOKU UNIV, SCH MED, DEPT DERMATOL, AOBA KU, 1-1 SEIRYO MACHI, SENDAI, MIYAGI 9808574, JAPAN (Reprint); TOHOKU UNIV, SCH MED, DEPT DERMATOL, AOBA KU, SENDAI, MIYAGI 9808574, JAPAN; BANARAS HINDU UNIV, INST MED SCI, DEPT DERMATOL, VARANASI 221005, UTTAR PRADESH, INDIA. ARCHIVES OF DERMATOLOGICAL RESEARCH (OCT 1999) Vol. 291, No. 10, pp. 548-554. Publisher: SPRINGER VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0340-3696. Pub. country: JAPAN; INDIA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB By their potent antigen-presenting function, dendritic cells (DCs) play a crucial role in the initiation of T cell-mediated immunity, including allergic contact hypersensitivity. To acquire such potent antigen-presenting ability, DCs in tissue must be activated, with increased expression of costimulatory molecules. Recent progress in DC biology has demonstrated that DCs can be activated via a variety of substances, e.g. various **cytokines**, CD40 ligand, bacterial products, and haptens, to increase their antigen-presenting ability, probably by different mechanisms. Therefore, in this study, to elucidate the mechanisms underlying the efficacy of the immunosuppressive drugs dexamethasone (DEX), cyclosporine A (CY), and **vitamin D**-3 (Vit D3) in the modulation of allergic contact hypersensitivity reactions, we examined the effects of these drugs on CD86 and HLA-DR antigen expression and TNF alpha secretion by monocyte-derived DCs stimulated with two representative haptens, NiCl2 and DNCB, in vitro. The augmented expression of CD86 induced by NiCl2 and DNCB was significantly

suppressed by DEX at concentrations in the range 10(-8) to 10(-5) M, which include concentrations less than its therapeutically effective concentration of 10(-7) M. Vit D3 also significantly suppressed NiCl2- and DNCB-induced augmented expression of CD86, at concentrations in the ranges 10(-9) to 10(-7) M and 10(-10) to 10(-7) M, respectively. In contrast, significant suppressive effects of CY on the NiCl2- or DNCB-induced augmented expression of CD86 were seen only at concentrations in the range 10(-6) to 10(-5) M, which are more than ten times higher than its effective concentration for T cell suppression. The augmented expression of HLA-DR antigen, which was only induced by stimulation with NiCl2, was resistant to treatment with these three drugs. Only DEX suppressed HLA-DR antigen expression at 10(-5) M. TNF alpha secretion by stimulated DCs was suppressed by DEX and Vit D3, although their effects were not statistically significant. Thus DEX and Vit D3 could modulate allergic contact dermatitis by their clearly demonstrated suppressive effects on the activation of DCs by haptens.

L21 ANSWER 4 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

97:904239 The Genuine Article (R) Number: YJ325. Increased presence of CD34(+) cells in the peripheral blood of head and neck cancer patients and their differentiation into dendritic cells. Garrity T; Pandit R; Wright M A; Benefield J; Keni S; Young M R I (Reprint). VET AFFAIRS EDWARD HINES JR HOSP, RES SERV 151Z2, HINES, IL 60141 (Reprint); VET AFFAIRS EDWARD HINES JR HOSP, RES SERV 151Z2, HINES, IL 60141; LOYOLA UNIV, SCH MED, DEPT OTOLARYNGOL, MAYWOOD, IL 60153; LOYOLA UNIV, STRITCH SCH MED, DEPT PATHOL, MAYWOOD, IL 60153. INTERNATIONAL JOURNAL OF CANCER (27 NOV 1997) Vol. 73, No. 5, pp. 663-669. Publisher: WILEY-LISS. DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012. ISSN: 0020-7136. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Patients with head and neck squamous cell carcinoma (HNSCC) have profound immune deficiencies. In 65% of these patients, there is an increased intra-tumoral presence of immune-suppressive CD34(+) progenitor cells. The goal of the present study was to determine whether CD34(+) cell levels were also increased in the peripheral blood of HNSCC patients and if these immune-suppressive cells could be differentiated into dendritic cells. Our results showed that CD34(+) cell levels are increased in the peripheral blood of HNSCC patients. To assess if these CD34(+) cells could differentiate into dendritic cells, they were isolated from the blood of HNSCC patients and cultured for 12 days with various **cytokine** combinations. Culturing CD34(+) cells with stem cell factor (c-kit ligand) plus granulocyte-macrophage colony-stimulating factor resulted in the appearance of a significant proportion of cells expressing phenotypic markers characteristic of dendritic cells. Also, including tumor necrosis factor-alpha yielded a significant proportion of cells resembling the bi-potential precursor cells for dendritic cells and monocytes (CD14(+)CD1a(+)), in addition to the dendritic-like cells. When the differentiation inducer 1 alpha,25-dihydroxyvitamin D-3 [1,25(OH)(2)D-3] was added along with the **cytokine** combinations, the yield of cells having characteristics of dendritic cells was further increased. Cells that were derived from CD34(+) cell cultures containing 1,25(OH)(2)D-3 had a more potent capacity to present the recall antigen tetanus toxoid to autologous peripheral blood leukocytes and to stimulate a mixed leukocyte response compared to cultures to which 1,25(OH)2D, had not been added. Our results show that CD34(+) cells, whose frequency is increased in HNSCC patients, can be differentiated into cells that phenotypically and functionally resemble dendritic cells and that 1,25(OH)(2)D-3 accentuates this differentiation. (C) 1997 Wiley-Liss, Inc.

L21 ANSWER 5 OF 7 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1

94184909 EMBASE Document No.: 1994184909. Immunosuppressive effects of 1.25-dihydroxyvitamin D3 and its analogue calcipotriol on epidermal cells. Bagot M.; Charue D.; Lescs M.-C.; Pamphile R.; Revuz J.. Department of Dermatology, Henri Mondor Hospital, 51 Av. Marechal de Lattre

Tassigny,94010 Creteil, France. British Journal of Dermatology 130/4 (424-431) 1994.
ISSN: 0007-0963. CODEN: BJDEAZ. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3: calcitriol) is the biologically active form of **vitamin D**. This hormone is a potent immunoregulatory agent. Calcipotriol is a synthetic analogue of 1,25(OH)2D3, with similar receptor binding, and comparable effects on cell proliferation and differentiation, but less potent effects on calcium metabolism. As a step towards understanding the mechanisms by which **vitamin D** compounds affect T-cell activation by epidermal cells (EC), we assessed the effects of 1,25(OH)2D3 and calcipotriol on the human allogeneic mixed epidermal cell-lymphocyte reaction. All experiments were performed both with 1,25(OH)2D3, and calcipotriol, with similar results. Both compounds had potent immunoinhibitory properties on this model, and enhanced the immunosuppressive effects of cyclosporin A. Using preincubation experiments, we found that pretreatment of EC with 1,25(OH)2D3 resulted in a more pronounced inhibition than preincubation of lymphoid cells. The epidermal targets of this inhibitory effect have been further investigated, using cultures with freshly isolated **Langerhans cells** (LC) or LC-depleted keratinocytes, separated by an immunomagnetic particle technique. Pretreatment of LC induced a 30% decrease of proliferation, compared with vehicle-treated LC. These calcitriol-pulsed LC did not decrease the proliferation induced by unmodified autologous EC. As expected, LC-depleted keratinocytes failed to stimulate allogeneic lymphocytes. When added to autologous unmodified EC, however, calcitriol-pulsed keratinocytes induced an 85% decrease of proliferation, compared with vehicle-treated keratinocytes. The phenotypic expression of HLA-DR, -DQ, and -DP antigens on EC, assessed by immunoalkaline phosphatase staining, was not modified after a 2-h or 24-h pulse with 1,25(OH)2D3 or calcipotriol. The inhibitory effect of **vitamin D** compounds on EC was not modified by indomethacin, but was partially reversed by the addition of anti-TGF-.beta. neutralizing antibodies. In conclusion, 1,25(OH)2D3 and calcipotriol may limit the immune response in human skin through decreased antigen presentation, mediated both by a direct effect on LC and indirectly through modulation of the production of **cytokines** by keratinocytes.

L21 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1994:379866 Document No.: PREV199497392866. Sun, melanogenesis, and **cytokines**. Levine, N.. Sect. Dermatol., Univ. Arizona, Tucson, AZ 85724, USA. Photochemistry and Photobiology, (1994) Vol. 59, No. SPEC. ISSUE, pp. 3S.
Meeting Info.: 22nd Annual Meeting of the American Society for Photobiology. Scottsdale, Arizona, USA. June 25-29, 1994.
CODEN: PHCBAP. ISSN: 0031-8655. Language: English.

L21 ANSWER 7 OF 7 MEDLINE on STN
89235902 Document Number: 89235902. PubMed ID: 3149987. Photoimmunology: the mechanisms involved in immune modulation by UV radiation. Roberts L K; Smith D R; Seilstad K H; Jun B D. (Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City 84132.) JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY. B, BIOLOGY, (1988 Sep) 2 (2) 149-77. Ref: 148. Journal code: 8804966. ISSN: 1011-1344. Pub. country: Switzerland. Language: English.

AB Ultraviolet radiation (UVR) may be the most prevalent agent that man encounters in his environment. As a result, certain biological adaptations take advantage of the beneficial effects of UVR exposure, e.g. the photoactivation steps involved in **vitamin D** metabolism. In this regard, UVR plays an important role in maintaining our good health; however, it must be noted that UVR is potentially the most harmful naturally occurring agent in our environment. Thus, it appears that several mechanisms have evolved to protect us against the

detrimental effects of UVR overexposure. Although epidermal melaninization or "tanning" may be the most obvious example of these processes, we would argue that adoptive mechanisms within the immune system also provide protection against UVR-induced skin damage. It is now known that UVR affects the distribution and functional activities of various immunocompetent cells within the skin, as well as modifying the production of inflammatory and hematopoietically active **cytokines** . This review will focus on the known mechanisms involved in the immune modulatory effects of UVR and how adoptive immune responses to UVR-induced skin damage contribute to specific pathological processes.

=> s (geissmann f?/au or lepelletier y?/au or dy m?/au or durandy a?/au or revy p?/au or chambon p?/au)
L22 5293 (GEISSMANN F?/AU OR LEPELLETIER Y?/AU OR DY M?/AU OR DURANDY A?/AU OR REVY P?/AU OR CHAMBON P?/AU)

=> s l22 and antigen presenting cell
L23 27 L22 AND ANTIGEN PRESENTING CELL

=> s l23 and vitamin D
L24 0 L23 AND VITAMIN D

=> s l23 and retinoids
L25 1 L23 AND RETINOIDS

=> d l25 cbib abs

L25 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
2001:780660 Document No. 135:327340 Retinoid compositions and methods for use in modulating immune system function. **Geissmann, Frederic**; **Lepelletier, Yves**; **Dy, Michel**; **Durandy, Anne**; **Revy, Patrick**; **Chambon, Pierre** (Fr.). PCT Int. Appl. WO 2001078700 A2 20011025, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-IB484 20010412. PRIORITY: US 2000-PV196921 20000413.

AB Vitamin A (retinol) deficiency results in impaired response to infection and increased mortality. The inventors show that retinol activates immature dendritic cells (DC) and enhances antigen presentation via a cross-talk with inflammatory cytokines, whereas it increases DC death in the absence of these cytokines. These effects, that are mediated through retinoic acids and distinct nuclear retinoid receptor pathways, can be dissocd. from each other with selective synthetic **retinoids**. The invention identifies a novel cellular target and function for **retinoids**, provides compns. and methods for modulating the immune system and for treating or preventing various phys. disorders in animals, preferably via controlling activation and/or apoptosis in **antigen -presenting cells** using selective **retinoids**.

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L26 12 DUP REMOVE L23 (15 DUPLICATES REMOVED)

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L26 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
2003:334932 Document No. 138:348703 Neuropilin as a therapeutic target for

modulation of immune responses. Tordjman, Rafaele; **Lepelletier, Yves**; Romeo, Paul-Henri; Hermine, Olivier (Institut National De La Sante Et De La Recherche Medicale (INSERM), Fr.). PCT Int. Appl. WO 2003035100 A1 20030501, 85 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IB4596 20020926. PRIORITY: EP 2001-402474 20010926.

AB The invention provides methods that enable the identification of modulators of immune responses mediated by immune effective cells, esp. of the initiation of primary immune responses, and to methods for treating and/or preventing diseases or pathol. conditions assocd. with or controlled by the immune responses. More specifically, the invention provides methods for identifying compds. that modulate the selective interaction between cells implicated in the immune response and/or that induce or inhibit the recruitment of semaphorin by neuropilin receptor and that are useful for modulating the immune response mediated by immune effective cells.

L26 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 1

2003308752 Document Number: 22720729. PubMed ID: 12836215. [Immunological synapses and neuronal synapses]. Synapses immunologiques et synapses neuronales. Trautmann Alain; **Revy Patrick**; Donnadieu Emmanuel; Bismuth Georges. (Departement de Biologie Cellulaire, Institut Cochin, Inserm U.567, Cnrs UMR 8104, 22, rue Mechain, 75014 Paris, France.. trautmann@cochin.inserm.fr) . Med Sci (Paris), (2003 Apr) 19 (4) 429-36. Ref: 56. Journal code: 8710980. ISSN: 0767-0974. Pub. country: France. Language: French.

AB The interface between two cells from the immune system has recently been coined "immunological synapse". The authors review recent findings concerning the structure of the synapse formed between T lymphocytes and **antigen-presenting cells**. T cells can be part of different synapses, depending on the **antigen-presenting cell** (B cell hybridoma, proteo-lipid bilayer, macrophage, dendritic cell). The synapse formed with dendritic cells is discussed in more details. A comparison is made with the synapses from the nervous system. Several parallel questions are discussed: how receptors can be clustered, what is the influence of synapse functioning on the structure of the synapse. It is suggested that in both cases two modes of communication exist in parallel: direct cell-cell contacts and soluble mediators, neurotransmitters in one case, putative immunotransmitters in the other.

L26 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN

2001:780660 Document No. 135:327340 Retinoid compositions and methods for use in modulating immune system function. **Geissmann, Frederic**; **L pelletier, Yves**; **Dy, Michel**; **Durandy, Anne**; **R vy, Patrick**; **Chambon, Pierre** (Fr.). PCT Int. Appl. WO 2001078700 A2 20011025, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-IB484 20010412. PRIORITY: US 2000-PV196921 20000413.

AB Vitamin A (retinol) deficiency results in impaired response to infection and increased mortality. The inventors show that retinol activates

immature dendritic cells (DC) and enhances antigen presentation via a cross-talk with inflammatory cytokines, whereas it increases DC death in the absence of these cytokines. These effects, that are mediated through retinoic acids and distinct nuclear retinoid receptor pathways, can be dissocd. from each other with selective synthetic retinoids. The invention identifies a novel cellular target and function for retinoids, provides compns. and methods for modulating the immune system and for treating or preventing various phys. disorders in animals, preferably via controlling activation and/or apoptosis in **antigen-presenting cells** using selective retinoids.

L26 ANSWER 4 OF 12 MEDLINE on STN DUPLICATE 2
2001535661 Document Number: 21467524. PubMed ID: 11582941. [Development of specific immunity in prenatal life]. Developpement de l'immunite specifique au cours de la vie prenatale. **Durandy A**. (Inserm U429, hopital Necker-Enfants-Malades, 149, rue de sevres, 75015 Paris, France.. durandy@necker.fr) . ARCHIVES DE PEDIATRIE, (2001 Sep) 8 (9) 979-85. Ref: 37. Journal code: 9421356. ISSN: 0929-693X. Pub. country: France. Language: French.

AB The various defense mechanisms of specific immunity, which involves the T and B lymphocytes and the **antigen presenting cells**, are gradually developed during intra-uterine life. The first hematopoietic organ is the yolk sac which appears at the 4th week of development. Thereafter, the hematopoiesis takes place in the fetal liver (from the 6th week) followed by the bone-marrow during the 3rd trimester. The differentiation of the T lymphocytes begins around the 10th week. The thymic epithelial rudiments appear during the 7th week and the thymus migrates to its definitive place at ten weeks. It is then colonized by the T cell precursors, which there undergo their maturation process. From the 12th week of development, mature T cells are readily detectable in lymphoid organs and fetal blood. The maturation of B cells, which occurs firstly in fetal lever, and thereafter in bone marrow begins also early in fetal life (12th week). The **antigen presenting cells**, the precursors of which are detected in the yolk sac as soon as 4-6 weeks, are normally present and functional in secondary lymphoid organs as soon as 12 weeks. Thus, the specific immune response appears possible by the end of the 1st trimester. However, the naive nature of T and B lymphocytes is responsible for a delayed, slow and relatively ineffective primary response. This observation explains the particular susceptibility of neonates, especially premature neonates to bacterial and viral infections. The various antigenic stimulations and T/B cell cooperations allow a complete maturation of the immune system during the first years of life.

L26 ANSWER 5 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2001:429054 Document No.: PREV200100429054. Imaging T-cell antigen recognition and comparing immunological and neuronal synapses. Donnadieu, Emmanuel; **Revy, Patrick**; Trautmann, Alain [Reprint author]. Laboratoire d'Immuno-Pharmacologie, CNRS UPR 415, ICGM, 22 Rue Mechain, Bat Gustave-Roussy, 75014, Paris, France. trautmann@cochin.inserm.fr. Immunology, (August, 2001) Vol. 103, No. 4, pp. 417-425. print. CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L26 ANSWER 6 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3
2000075389 EMBASE [Development of the specific immune system in the foetus and neonate]. DEVELOPPEMENT DU SYSTEME IMMUNITAIRE SPECIFIQUE CHEZ LE FOETUS ET LE NOUVEAU-NE. **Durandy A.**. Dr. A. Durandy, Svc. d'Immunologie et d'Hematologie, Hopital Necker Enfants Malades, INSERM U 429, 149, rue de Sevres, 75015 Paris, France. Revue Francaise d'Allergologie et d'Immunologie Clinique 40/1 (65-69) 2000. Refs: 20.
ISSN: 0335-7457. CODEN: RFAIBB. Pub. Country: France. Language: French. Summary Language: English; French.

AB The various defence mechanisms of specific immunity are gradually

developed during intra-uterine life. The differentiation of T and B lymphocytes and **antigen-presenting cells**, necessary for the specific immune response, begins very rapidly during pregnancy and a specific response appears possible by 12 weeks. However, the naive nature of T and B lymphocytes is responsible for a delayed, slow and relatively ineffective primary response, which explains the particular susceptibility of neonates, especially premature neonates, to viral and bacterial infections. The various antigenic stimulations and T/B cell cooperations allow complete maturation of the immune system during the first years of life.

L26 ANSWER 7 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

97380069 EMBASE Document No.: 1997380069. Development of the immune system. **Durandy A.**. A. Durandy, Inst. Natl Sante Recherche Med. U429, Hopital Necker-Enfants Malades, 149 rue de Sevres, 75743 Paris Cedex 15, France. Infectious Disease in Obstetrics and Gynecology 5/2 (93-97) 1997.
Refs: 27.
ISSN: 1064-7449. CODEN: IDOGEX. Pub. Country: United States. Language: English.

L26 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 4

1998038284 Document Number: 98038284. PubMed ID: 9370950. Epidermal Langerhans' cells in children with primary T-cell immune deficiencies. Emile J F; **Durandy A**; Le Deist F; Fischer A; Brousse N. (Service d'anatomie et de cytologie pathologiques, Hopital Necker-Enfants Malades, Paris, France.. jfemile@club-internet.fr) . JOURNAL OF PATHOLOGY, (1997 Sep) 183 (1) 70-4. Journal code: 0204634. ISSN: 0022-3417. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Dendritic cells are the major **antigen-presenting cells**, especially for naive T lymphocytes; it is conceivable therefore that their absence or dysfunction may induce an immune deficiency (ID). Few data are available, however, concerning dendritic cells in human primary ID. Langerhans' cells (LC) are intraepidermal dendritic cells which express specific markers and may therefore be studied by immunohistochemistry on paraffin-embedded skin samples. Skin samples of nine children with primary ID were studied and compared with five age-matched controls. LC were present within the epidermis of two children with X-linked severe combined ID, a condition related to the lack of the common gamma-chain of interleukin-2 (IL-2), IL-4, IL-7, IL-9, and IL-15 receptors. LC were also present in skin samples of a child with Omenn syndrome and in three children with combined ID. By contrast, no LC were detected in the skin samples of two children with alymphocytosis and of a child with reticular dysgenesis, a condition characterized by the absence of peripheral blood leukocytes.

L26 ANSWER 9 OF 12 MEDLINE on STN

94327929 Document Number: 94327929. PubMed ID: 8051402. Endogenous granulocyte-macrophage colony-stimulating factor is involved in IL-1- and IL-7-induced murine thymocyte proliferation. Herbelin A; Machavoine F; Vicari A; Schneider E; Papiernik M; Ziltener H; Penit C; **Dy M**. (INSERM U 25, Necker Hospital, Paris, France.) JOURNAL OF IMMUNOLOGY, (1994 Sep 1) 153 (5) 1973-81. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We have reported previously that IL-1 induces murine thymocyte proliferation in the absence of artificial comitogens, provided that the cells are cultured at high densities. In the present study, we show that, in these conditions, TdR uptake in response to IL-1 is diminished significantly by anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) Abs. Indeed, a substantial production of this growth factor occurs when thymocytes are cultured in the presence of IL-1. Maximal GM-CSF levels are attained within 3 days of culture, and mRNA expression is detected after a 48-h stimulation. Both GM-CSF production and IL-1-induced thymocyte proliferation are decreased considerably by the

depletion of I-A+ Mac-1+ accessory cells. Yet, addition of exogenous GM-CSF to accessory cell-depleted thymocytes does not restore the proliferative response to IL-1 alone, suggesting the implication of another accessory cell-derived mediator. Our data design IL-7 as the endogenous factor required in our culture system because: 1) GM-CSF can reverse the decrease in the proliferation after accessory cell depletion when IL-7 is provided together with IL-1, and 2) the proliferative response to IL-1 plus IL-7 is diminished as much by neutralization of GM-CSF by its specific Abs as by accessory cell removal (approximately 30%). Finally, the cells responding to IL-1 + IL-7 were identified as mature CD4-CD8-TCR+ thymocytes by the use of bromodeoxyuridine (BrdUrd), suggesting that the GM-CSF produced by thymic accessory cells in response to IL-1 participates in IL-7-dependent, intrathymic expansion of the CD4-CD8-TCR+ compartment.

L26 ANSWER 10 OF 12 MEDLINE on STN

92091800 Document Number: 92091800. PubMed ID: 1727878. IL-7 is requisite for IL-1-induced thymocyte proliferation. Involvement of IL-7 in the synergistic effects of granulocyte-macrophage colony-stimulating factor or tumor necrosis factor with IL-1. Herbelin A; Machavoine F; Schneider E; Papiernik M; **Dy M**. (INSERM U 25, Hopital Necker, Paris, France.) JOURNAL OF IMMUNOLOGY, (1992 Jan 1) 148 (1) 99-105. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB In the absence of artificial comitogens murine thymocytes proliferate significantly in response to IL-1 at high but not at low cell densities. This observation has led us to examine a possible indirect mechanism requiring other thymocyte-growth factors, such as IL-2, IL-4, IL-6, and IL-7, in this phenomenon. Our data provide evidence that IL-7 is requisite for the IL-1-induced proliferative response because on the one hand the growth-promoting activity of IL-1 is completely inhibited by an anti-IL-7 mAb, and on the other hand IL-7 synergizes with IL-1 on thymocyte growth. This synergy is observed even at concentrations at which IL-7 is not detected in the pre-B cell proliferation assay, and results, at optimal doses, in TdR incorporation levels similar to those attained in response to IL-1 + IL-2. The anti-IL-7 mAb acts in a dose-dependent manner and does not affect other activities of IL-1, such as its capacity to sustain the growth of the U373 astrocytoma cell line. It is also noteworthy that this mAb does not significantly impair thymocyte growth in response to IL-2 and that the growth-promoting activity of IL-1 is not affected by neutralizing mAb against IL-2, IL-4, and IL-6. In addition, we show that the potentiating effect of granulocyte-macrophage (GM)-CSF and TNF-alpha on IL-1-induced thymocyte growth is dependent on IL-7 because i) the anti-IL-7 mAb abrogates the respective synergistic interactions and ii) both factors potentiate the proliferative response to IL-7. Finally, depletion of thymocyte suspensions for Ia+ Mac-1+ accessory cells results in a considerable decrease in IL-1- and IL-1 + GM-CSF-induced TdR uptake, whereas IL-7-induced growth remains unchanged. Taken together, these results support the notion that, in the absence of artificial comitogens, thymocyte proliferation in response to IL-1 alone or in combination with GM-CSF is dependent on accessory cell-derived IL-7.

L26 ANSWER 11 OF 12 MEDLINE on STN DUPLICATE 5

86169667 Document Number: 86169667. PubMed ID: 3514755. Role of the LFA-1 molecule in cellular interactions required for antibody production in humans. Fischer A; **Durandy A**; Sterkers G; Griscelli C. JOURNAL OF IMMUNOLOGY, (1986 May 1) 136 (9) 3198-203. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The lymphocyte function-associated antigen 1 (LFA-1) has been shown to play a role in various T cell functions in mice and humans including cytotoxicity, and proliferation to allogeneic cells and foreign antigens. These functions have been defined with specific monoclonal antibodies and were additionally confirmed by the investigation of patients with inherited deficiency in membrane LFA-1 expression. In this paper, we report our studies on the potential role of the LFA-1 molecule in T

lymphocyte-dependent antibody responses. In a patient with a complete lack of membrane expression of LFA-1, there was no in vivo antibody response to vaccinal antigens such as tetanus, diphtheria toxoids, and polio virus, and no in vivo or in vitro antibody production to influenza virus, whereas serum immunoglobulin levels and antibodies to polysaccharides (isohemagglutinins, antibody to mannan, and a polysaccharide from Candida albicans) were detected in correlation with in vitro production of anti-mannan antibody. The defective antibody response to polypeptides was not secondary to poor antigen-specific T proliferation, because the latter was found to be present. Similarly, in vitro antibody production to influenza virus of normal cells was blocked by several anti LFA-1 monoclonal antibodies specific for the alpha subunit of the molecule, if they were added from the beginning of the culture. The antibody production blockade could be achieved with monoclonal antibody concentrations that partially preserved T cell proliferation. The helper effect of an influenza virus-specific helper T cell clone was also blocked. The targets of the blockade were shown by incubation experiments to be T cells and monocytes. In contrast, anti-LFA-1 monoclonal antibodies had no effect on pokeweed mitogen-induced B cell maturation into immunoglobulin-containing cells and on the anti-mannan antibody production. These combined data demonstrate that the LFA-1 molecule plays a role in T cell dependent antibody production to polypeptidic antigens but not in the antibody response to polysaccharides, although the antibody response to mannan is T cell dependent. It is proposed that the LFA-1 molecule is required to some extent for a **antigen-presenting cells**-T lymphocyte interaction and for the maintenance of a close association between antigen-specific helper T cells and small resting B lymphocytes. Polysaccharidic antigens that exhibit repetitive antigenic determinants might cross-link membrane immunoglobulins on B lymphocytes, thus allowing B cells to pass through a first step of activation requiring cognate T-B cell interaction.

L26 ANSWER 12 OF 12 MEDLINE on STN DUPLICATE 6

85230913 Document Number: 85230913. PubMed ID: 3159585. HLA class II restriction governing cell cooperation between antigen-specific helper T lymphocytes, B lymphocytes and monocytes for in vitro antibody production to influenza virus. Fischer A; Sterkers G; Charron D; **Durandy A.** *EUROPEAN JOURNAL OF IMMUNOLOGY*, (1985 Jun) 15 (6) 620-6. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB To study HLA class II compatibility requirement for in vitro antibody production to influenza virus, semipurified T lymphocytes, B lymphocytes and monocytes from HLA-typed responder donors were used. The presence of the three subpopulations was required for antibody production while a mixture of only two of those was ineffective. When using fresh T lymphocytes which exert an allogeneic suppressive effect and may also exhibit allogeneic helper activity, it was not possible to conclude an HLA class II-linked restriction of T-B cell cooperation although there was a suggestion of it. However, a grown H3 hemagglutinin-specific T cell line (L2), previously shown to be restricted by HLA-DR molecule (DR1) for interaction with **antigen-presenting cells** and devoid of allogeneic reactivity, exerts an HLA class II-restricted helper activity. This was demonstrated by various combinations of HLA-DR semi-compatible or incompatible B lymphocytes and/or monocytes with L2 T cells. The restriction element was identified as an HLA-DR determined since HLA-DC-compatible, HLA-DR-incompatible B lymphocytes were not helped by L2 T cells. In addition, monoclonal anti-HLA-DR but not anti-HLA-DC antibodies directed to the relevant specificity did inhibit the antigen-specific helper activity. We present evidence that not only T monocyte but also T-B and/or T-B-monocyte interactions are HLA class II restricted.

=> s l2 and apoptosis

L27 1843 L2 AND APOPTOSIS

=> s l27 and retinoid
L28 17 L27 AND RETINOID

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L29 13 DUP REMOVE L28 (4 DUPLICATES REMOVED)

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L29 ANSWER 1 OF 13 MEDLINE on STN DUPLICATE 1
2002353984 Document Number: 22091948. PubMed ID: 12097298. Cyclin B and E2F-1 expression in prostate carcinoma cells treated with the novel **retinoid** CD437 are regulated by the ubiquitin-mediated pathway.
Farhana Lulu; Dawson Marcia; Rishi Arun K; Zhang Yuxiang; Van Buren Eric; Trivedi Charu; Reichert Uwe; Fang Guowei; Kirschner Marc W; Fontana Joseph A. (John D. Dingell VA Medical Center and Karmanos Cancer Institute, and Department Internal Medicine, Wayne State University, Detroit, Michigan 48201, USA.) CANCER RESEARCH, (2002 Jul 1) 62 (13) 3842-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB E2F-1 and cyclin B are important regulators of the cell cycle, and their expressionand degradation are tightly regulated. Proteolysis of both molecules is mediated by the ubiquitin degradation pathway involving the activation of specific E3 ubiquitin ligases. Treatment of prostate carcinoma cells with the novel **retinoid** 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437/AHPN) results in the enhanced expression of E2F-1 and rapid degradation of cyclin B in the absence of the modulation of mRNA levels; this is accompanied by the S phase arrest of the cells and subsequent **apoptosis**. The elevated level of E2F-1 is because of the enhanced stability of the molecule, as indicated by pulse-labeling studies, demonstrating a prolonged half-life. The enhanced E2F-1 stability is associated with the concomitant acetylation of E2F-1, the disassociation of E2F-1 from the E2F-1 E3 ligase p45(SKP2), and decreased E2F-1 ubiquitination, suggesting CD437 inhibition of E-3 E2F-1 ligase activity. Exposure of the cells to CD437 also results in the enhanced association of the cyclin B E3 ligase **APC** with cyclin B and the rapid proteolysis of cyclin B. The CD437-enhanced proteolysis of cyclin B is blocked in the presence of the ubiquitin proteolysis inhibitor N-acetyl-leu-leu-norleu-al. Thus, CD437 modulates the expression of E2F-1 and cyclin B through the simultaneous stimulation and inhibition of the cyclin B and E2F-1 E3 ligases, respectively.

L29 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:394473 Document No.: PREV200200394473. Preventive efficacy of 9 cis retinoic acid on mutant colon epithelial cell lines established from **APC**(+/-)1638N and MLH1(+/-)/1638N(+/-) gene knockout mice.
Katdare, Meena [Reprint author]; Kopelovich, Levy; Telang, Nitin T.. Rockefeller University, New York, NY, USA. Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 124. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X. Language: English.

L29 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN
2001:828415 Document No. 137:89412 Detection of variations in the DNA methylation profile of genes in the determining the risk of disease.
Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander (Epigenomics A.-G., Germany). PCT Int. Appl. WO 2001077373 A2 20011018, 636 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,

TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-XA1486 20010406. PRIORITY: DE 2000-10019058 20000406; WO 2001-DE1486 20010406.

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for detg. the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for detg. the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or assocd. syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. This abstr. record is one of several records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.

L29 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

2001:338762 Document No. 134:362292 Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile. Farr, Spencer (Phase-1 Molecular Toxicology, USA). PCT Int. Appl. WO 2001032928 A2 20010510, 222 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30474 20001103. PRIORITY: US 1999-PV165398 19991105; US 2000-PV196571 20000411.

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

L29 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

2001:137420 Document No. 134:188194 PPAR.delta. links **APC** to chemopreventive drugs. He, Tong-Chuan; Kinzler, Kenneth W.; Vogelstein, Bert (The Johns Hopkins University, USA). PCT Int. Appl. WO 2001012858 A1

20010222, 70 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US22411 20000816. PRIORITY: US 1999-PV148701 19990816.

AB PPAR.delta. was identified as a target of **APC** suppression through the anal. of global gene expression profiles in human colorectal cancer cells. PPAR.delta. expression is elevated in primary colorectal cancers and significantly repressed by **APC** in colorectal cancer cells. This repression is mediated by two Tcf-4-responsive elements in the PPAR.delta. promotor. Reporters contg. PPAR.delta.-responsive elements are repressed by sulindac, a non-steroidal anti-inflammatory (NSAID) agent which can reduce the size and no. of colon tumors in humans and animals with **APC** mutations. Furthermore, sulindac is able to specifically disrupt the ability of PPAR.delta. to bind its cognate recognition sequences. These findings suggest a model wherein NSAIDs inhibit tumorigenesis through post-transcriptional modification of a gene that is normally regulated by **APC**. This novel mol. target for NSAIDs can be used to develop more effective chemopreventive agents for colorectal tumors.

L29 ANSWER 6 OF 13 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

2002:163710 The Genuine Article (R) Number: BT69J. Chemopreventive agents inhibit aberrant proliferation of the aneuploid phenotype in a colon epithelial cell line established from **Apc** 1638N [+/-] mouse. Katdare M; Kopelovich L; Telang N (Reprint). Rockefeller Univ, Strang Canc Res Lab, 1230 York Ave, New York, NY 10021 USA (Reprint); Strang Canc Prevent Ctr, Chemoprevent Res Lab, New York, NY 10021 USA; NCI, Chemoprevent Branch, Bethesda, MD 20852 USA. CANCER PREVENTION (25 FEB 2001) Vol. 952, pp. 169-174. Publisher: NEW YORK ACAD SCIENCES. 2 EAST 63RD ST, NEW YORK, NY 10021 USA. ISSN: 0077-8923. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Loss of function of the adenomatous polyposis coli (**APC**) tumor suppressor gene predisposes for familial adenomatous polyposis (FAP) syndrome. The Ape gene knockout mice exhibit accelerated intestinal carcino-gensis modifiable by diverse pharmacological agents. Present experiments utilized the Ape[+/-] 1638N COL colon epithelial cell line (origin: histologically normal colon) as the model. **Retinoid** receptor modulator 9-cis-retinoic acid (9-cis-RA), ornithine decarboxylase inhibitor difluoromethyl ornithine (DFMO), and nonselective cyclooxygenase inhibitor sulindac (SUL) represented the chemopreventive test compounds. Population doubling, cell cycle progression, and anchorage-independent growth provided mechanistic end points for chemopreventive efficacy. Treatment of 1638N COL cells with 9-cis-RA, DFMO and SUL produced a dose-dependent cytostatic growth arrest by decreasing the number of population doublings and altering aneuploid G(0)/G(1):S+G(2)/M ratio. The clonally expanded 1638N-Cl-1 cells selected for anchorage-independent growth exhibited decreased anchorage-independent colony formation in response to treatment with the three test compounds. Susceptibility of preneoplastic 1638N COL cells to mechanistically distinct chemopreventive agents validates a unique epithelial cell culture model for FAP syndrome, and facilitates investigations on **Apc** regulated colon carcinogenesis and cancer Prevention.

L29 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

2001:464535 Document No. 136:68190 Time course of LPS-induced gene expression in a mouse model of genitourinary inflammation. Saban, Marcia R.; Hellmich, Helen; Nguyen, Ngoc-Bich; Winston, John; Hammond, Timothy G.; Saban, Ricardo (Department of Physiology, University Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA). Physiological Genomics

[online computer file], 5(3), 147-160 (English) 2001. CODEN: PHGEFP. ISSN: 1094-8341. URL: http://physiolgenomics.physiology.org/cgi/reprint/5/3/147 Publisher: American Physiological Society.

AB In this study, self-organizing map (SOM) gene cluster techniques are applied to the anal. of cDNA microarray anal. of gene expression changes occurring in the early stages of genitourinary inflammation. We detd. the time course of lipopolysaccharide (LPS)-induced gene expression in exptl. cystitis. Mice were euthanized 0.5, 1, 4, and 24 h after LPS instillation into the urinary bladder, and gene expression was detd. using four replicate Atlas mouse cDNA expression arrays contg. 588 known genes at each time point. SOM gene cluster anal., performed without preconditions, identified functionally significant gene clusters based on the kinetics of change in gene expression. Genes were classified as follows: 1) expressed at time 0; 2) early genes (peak expression between 0.5 and 1 h); and 3) late genes (peak expression between 4 and 24 h). One gene cluster maintained a const. level of expression during the entire time period studied. In contrast, LPS treatment down regulated the expression of some genes expressed at time 0, in a cluster including transcription factors, protooncogenes, **apoptosis**-related proteins (cysteine protease), intracellular kinases, and growth factors. Gene upregulation in response to LPS was obsd. as early as 0.5 h in a cluster including the interleukin-6 (IL-6) receptor, .alpha.- and .beta.-nerve growth factor (.alpha.- and .beta.-NGF), vascular endothelial growth factor receptor-1 (VEGF R1), C-C chemokine receptor, and P-selectin. Another tight cluster of genes with marked expression at 1 h after LPS and insignificant expression at all other time points studied included the protooncogenes c-Fos, Fos-B, Fra-2, Jun-B, Jun-D, and Egr-1. Almost all interleukin genes were upregulated as early as 1 h after stimulation with LPS. Nuclear factor-.kappa.B (NF-.kappa.B) pathway genes collected in a single cluster with a peak expression 4 h after LPS stimulation. In contrast, most of the interleukin receptors and chemokine receptors presented a late peak of expression 24 h after LPS coinciding with the peak of neutrophil infiltration into the bladder wall. Selected cDNA microarray observations were confirmed by RNase protection assay. In conclusion, the cDNA array exptl. approach provided a global profile of gene expression changes in bladder tissue after stimulation with LPS. SOM techniques identified functionally significant gene clusters, providing a powerful tech. basis for future anal. of mechanisms of bladder inflammation.

L29 ANSWER 8 OF 13 MEDLINE on STN

2002069863 Document Number: 21653732. PubMed ID: 11795445. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. Lamprecht S A; Lipkin M. (Strang Cancer Prevention Center, New York, NewYork 10021, USA.) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2001 Dec) 952 73-87. Ref: 128. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Convincing evidence is available showing that dietary calcium and vitamin D impede the development of colonic carcinogenesis. The major cellular modes of action of calcium and vitamin D which can contribute to the inhibition of colonic neoplasia are reviewed in this article. These consist of complex series of signaling events induced by the chemopreventive agents acting at various tiers of colonic cell organization.

L29 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

2000:314864 Document No. 132:344076 Method for detecting endocrine disruptor-responsive genes and for screening endocrine disruptors. Kondo, Akihiro; Sagawa, Hiroaki; Mineno, Junichi; Kimizuka, Fusao; Kato, Ikunoshin (Takara Shuzo Co., Ltd., Japan). PCT Int. Appl. WO 2000026404 A1 20000511, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM,

CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP5964 19991028. PRIORITY: JP 1998-310285 19981030.

AB A method and compns. for detecting genes affected by endocrine-disrupting chems. and for identifying endocrine-disrupting chems. are claimed. The method comprises prepg. a nucleic acid sample contg. mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample contg. the endocrine disruptor. The nucleic acid sample is hybridized with DNA arrays wherein genes which might be affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Endocrine disruptors are selected from dioxins, org. chloro compds., phenols, futalic acid esters, arom. hydrocarbons, agrochems., org. tin compds., and estrogens, among others. The effect of 3 chems., 17-.beta. estradiol (E2), diethylstilbestrol (DES), and bisphenol A (BisA) on 33 candidate genes belonging to the categories of nuclear receptor/nuclear receptor transcriptional coupling, kinase-type signal transducer, gonad differentiation factor, oncogene, and receptor-type kinase, were examd. by the method of this invention. Expression of most of the genes was either increased or decreased by exposure to these chems.

L29 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

2000:475956 Document No. 133:100426 Fusion proteins of ligand-binding domains and dimerization domains and their uses. Jerome, Valerie; Sedlacek, Hans-Harald; Mueller, Rolf (Aventis Pharma Deutschland G.m.b.H., Germany). Ger. Offen. DE 19900743 A1 20000713, 36 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1999-19900743 19990112.

AB Fusion proteins of ligand-binding domains and dimerization domains that can form complexes are described. The proteins have a ligand-binding domain fused to a dimerization domain that is derived from a naturally-occurring domain but is modified. The modifications are used to confer specificity of binding of the dimerization domain to a different dimerization domain that is also a deriv. of a naturally-occurring dimerization domain. The proteins have a range of uses where specific and regulatable protein interactions are needed, e.g. in the regulation of gene expression, as anal. reagents, in drug and DNA targeting. Expression constructs for the manuf. of these proteins are described. The construction of novel interacting pairs of fusion proteins is demonstrated.

L29 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

1999:795994 Document No. 132:31744 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Ltd., UK). PCT Int. Appl. WO 9964627 A2 19991216, 745 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1780 19990604. PRIORITY: GB 1998-12099 19980606; GB 1998-13291 19980620; GB 1998-13611 19980624; GB 1998-13835 19980627; GB 1998-14110 19980701; GB 1998-14580 19980707; GB 1998-15438 19980716; GB 1998-15576 19980718; GB 1998-15574 19980718; GB 1998-16085 19980724; GB 1998-16086 19980724; GB 1998-16921 19980805; GB 1998-17097 19980807; GB 1998-17200 19980808; GB 1998-17632 19980814; GB 1998-17943 19980819.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice

and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L29 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

1999:795993 Document No. 132:31743 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Limited, UK). PCT Int. Appl. WO 9964626 A2 19991216, 149 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1779 19990604. PRIORITY: GB 1998-12098 19980606; GB 1998-28289 19981223.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L29 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2003 ACS on STN

1999:529246 Document No. 131:168353 Identification of loci involved in accelerated wound healing and the development of new wound healing promoters. Heber-Katz, Ellen (The Wistar Institute, USA). PCT Int. Appl. WO 9941364 A2 19990819, 136 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,

TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US2962 19990212. PRIORITY: US 1998-PV74737 19980213; US 1998-PV97937 19980826; US 1998-PV102051 19980928.

AB Genes that quant. improve the efficiency and effectiveness of wound healing in mice are identified. Wound healing is assayed by measuring the time taken for a 2 mm hole punched into the ear to heal. The genes or gene products may be useful in the development of new wound healing promoters, including agents for treatment of central and peripheral nerve wounds. Wound healing in the rapidly healing mouse line MRL was studied. In comparison to the C57BL/6 line, the MRL mice showed more extensive vascularization around wounds with rapid development of sebaceous glands and hair follicles and the unexpected appearance of adipocytes. These mice also showed improved healing of damage to the optic and sciatic nerve after crushing, and of the spinal cord after complete transection. Using the difference in wound healing behavior of the two lines, genetic polymorphisms assocd. with QTLs affecting wound healing were identified. The accelerated healing of the MRL line was lost with aging, and this appeared to be as a result of T-cell actions. Macrophages from the MRL accelerated wound healing in control mice.

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=> s RAR agonist
L30         307 RAR AGONIST

=> s l30 and "APC"
L31           0 L30 AND "APC"

=> s l30 and antigen presenting cell
L32           5 L30 AND ANTIGEN PRESENTING CELL

=> dup remove l32
PROCESSING COMPLETED FOR L32
L33           1 DUP REMOVE L32 (4 DUPLICATES REMOVED)

=> d l33 cbib abs

L33  ANSWER 1 OF 1     MEDLINE on STN                    DUPLICATE 1
2003350905  Document Number: 22765440.    PubMed ID: 12882839.   Retinoic acids
     exert direct effects on T cells to suppress Th1 development and enhance
     Th2 development via retinoic acid receptors. Iwata Makoto; Eshima Yuko;
     Kagechika Hiroyuki. (Mitsubishi Kagaku Institute of Life Sciences, 11
     Minamiooya, Machida-shi, Tokyo 194-8511, Japan.. iwata@libra.Is.m-
     kagaku.co.jp) . INTERNATIONAL IMMUNOLOGY, (2003 Aug) 15 (8) 1017-25.
     Journal code: 8916182. ISSN: 0953-8178. Pub. country: England: United
     Kingdom. Language: English.
AB   The vitamin A metabolite, retinoic acid (RA), affects Th1 and Th2
     development. The effect is partly exerted through the modulation of
     antigen-presenting cell functions, but it
     remains unclear whether RA directly exerts its effect on T cells to
     influence Th1/Th2 development. To clarify this problem, we used two
     experimental systems with isolated T cells in vitro. In one system,
     isolated CD4+CD8+ thymocytes differentiated into Th1 and Th2 by two
     transient stimulations with defined combinations of ionomycin and phorbol
     myristate acetate followed by treatment with IL-2 and IL-4 and/or IL-12.
     In the second system, functional differentiation was induced in purified
     naive CD4 T cells from DO-11.10 TCR-transgenic and RAG-2-deficient mice
     with cytokines and antibodies to CD3 and CD28. In both systems,
     all-trans-RA at > or = 1 nM concentrations suppressed Th1 development, but
     enhanced Th2 development. 9-cis-RA elicited similar effects. The optimal
     enhancement of Th2 development in the second system, however, was achieved
     with a delayed addition of RA. The presence of RA during the initial
     stimulation period often suppressed Th2 development. The RA receptor
     (RAR) antagonists, LE540 and LE135, but not the retinoic X receptor (RXR)
     antagonist, PA452, inhibited the effect of RA on Th1/Th2 development.
     Accordingly, the RAR agonists, Am80 and Tp80, but not
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the RXR agonists, HX600 and TZ335, mimicked the effect of RA. The RXR agonists enhanced the effect of the **RAR agonists** only slightly, if at all. These results indicate that, via RAR, RA directly suppresses Th1 development and directly enhances Th2 development with its timely addition.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	250.11	250.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-22.79	-22.79

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